Clinical trial results:
A Phase III, Multicentre, Randomised, Double-Blind, Placebo-Controlled, 3-Arm Parallel Group Study to Determine the Efficacy and Safety of Lenalidomide (Revlimid) in Combination with Melphalan and Prednisone Versus Placebo Plus Melphalan and Prednisone in Subjects with Newly Diagnosed Multiple Myeloma Who Are 65 Years of Age or Older

Summary

EudraCT number	2006-001865-41
Trial protocol	NL BE FR DE IE CZ AT GB DK SE IT GR ES
Global end of trial date	13 April 2016

Results information

Result version number	v1 (current)
This version publication date	29 April 2017
First version publication date	29 April 2017

Trial information

Trial identification

Sponsor protocol code	CC-5013-MM-015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00405756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-290-1599, ClinicalTrialDisclosure@Celgene.com
Scientific contact	Annette Ervin-Haynes, Celgene Corporation, 01 908-673-9732, aervin-haynes@celgene.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	17 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of melphalan, prednisone and Revlimid (MPR) compared to placebo plus MP in subjects with newly diagnosed multiple myeloma (MM) who are 65 years of age or older.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 34
Country: Number of subjects enrolled	Austria: 23
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Georgia: 20
Country: Number of subjects enrolled	Germany: 60
Country: Number of subjects enrolled	Greece: 32
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 70
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Russian Federation: 20
Country: Number of subjects enrolled	Belarus: 5

Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Netherlands: 2
Worldwide total number of subjects	459
EEA total number of subjects	331

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	453
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This study was conducted in Europe, Australia, and Israel. Subjects were randomized at 82 sites (70 in Europe, 8 in Australia, and 4 in Israel). Subjects were ≥ 65 years old with newly diagnosed multiple myeloma who were ineligible for high-dose chemotherapy supported stem cell therapy.

Pre-assignment

Screening details:

Subjects were stratified at randomization by age (≤ 75 years versus > 75 years) and stage according to the International Staging System (ISS; Stages I or II versus Stage III)

Period 1

Period 1 title	Induction plus Maintenance Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The investigator, subject, and sponsor personnel responsible for the conduct of the study were blinded to each subject's treatment assignments during the subject's participation in the treatment period to minimize bias in the assessment of the data. The treatment assignment for each subject who discontinued the treatment period was unblinded by the investigator to guide future therapy. The blind was broken for those in the treatment period who were assessed by the investigator with PD.

Arms

Are arms mutually exclusive?	Yes
Arm title	Induction + Maintenance Phase: MPR+R

Arm description:

During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg by mouth (PO) daily (QD) on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on Days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle for up to 9 cycles (MPR), followed by maintenance therapy with single-agent lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle from cycle 10 until progressive disease (PD). If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.18 mg/kg tablet PO QD on days 1 to 4 of each 28-day cycle up to 9 cycles

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg capsule PO QD on Days 1 to 21 of each 28-day cycle up to 9 cycles during induction period and 10 mg capsule PO QD on Days 1 to 21 of each 28-day cycle from cycle 10 until disease progression

Investigational medicinal product name	Predisone
Investigational medicinal product code	
Other name	Prednisone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg/kg tablet PO QD on days 1 to 4 of each 28-day cycle up to 9 cycles

Arm title	Induction + Maintenance Phase: MPR+p

Arm description:

During the double-blind induction phase, participants received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles, followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD. If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.18 mg/kg tablet PO QD on days 1 to 4 of each 28-day cycle up to 9 cycles

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg capsule PO QD on Days 1 through 21 of each 28 day cycle for up to 9 cycles during induction period

Investigational medicinal product name	Predisone
Investigational medicinal product code	
Other name	Prednisone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg/kg tablet PO QD on days 1 to 4 of each 28-day cycle

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects in treatment arm MPR+p received placebo capsules PO QD on Days 1 through 21 of each 28-day cycle from cycle 10 until disease progression.

Arm title	Induction + Maintenance Phase: MPp+p

Arm description:

During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles (MPp), followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD. If participants experienced PD during the induction or maintenance treatment

periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Arm type	Active comparator
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.18 mg/kg tablet PO QD on days 1 to 4 of each 28-day cycle

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects in treatment arm MPp+p received placebo capsules PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles, followed by maintenance therapy with identically matching placebo capsules PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD.

Investigational medicinal product name	Predisone
Investigational medicinal product code	
Other name	Prednisone
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg/kg tablet PO on days 1 to 4 of each 28-day cycle

Number of subjects in period 1	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p
Started	152	153	154
Safety population	150 [1]	152 [2]	153 [3]
Completed Active Treatment Per Protocol	66 [4]	99 [5]	116 [6]
Completed	152	153	154

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was no defined completion for the induction-maintenance phase. Subjects continued in the induction-maintenance phase until disease progression, then were given the option to continue to the open-label extension phase.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was no defined completion for the induction-maintenance phase. Subjects continued in the induction-maintenance phase until disease progression, then were given the option to continue to the open-label extension phase.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: There was no defined completion for the induction-maintenance phase. Subjects continued in the induction-maintenance phase until disease progression, then were given the option to continue to the open-label extension phase, however, this was optional.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was no defined completion for the induction-maintenance phase. Subjects continued in the induction-maintenance phase until disease progression, then were given the option to continue to the open-label extension phase.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was no defined completion for the induction-maintenance phase. Subjects continued in the induction-maintenance phase until disease progression, then were given the option to continue to the open-label extension phase.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: There was no defined completion for the induction-maintenance phase. Subjects continued in the induction-maintenance phase until disease progression, then were given the option to continue to the open-label extension phase.

Period 2

Period 2 title	Open-label Extension Phase (OLEP)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MPR+R

Arm description:

Subjects who were treated with MPR+R and experienced PD during the induction or maintenance treatment periods were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg PO QD on Days 1 to 21 of each 28-day cycle

Arm title	MPR+p

Arm description:

Subjects who were treated with MPR+p and experienced PD during the induction or maintenance treatment periods were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg PO QD on Days 1 to 21 of each 28-day cycle

Arm title	MPp+p

Arm description:

Subjects who were treated with MPp+p and experienced PD during the induction or maintenance treatment periods were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Arm type	Active comparator
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25 mg PO QD on Days 1 to 21 of each 28-day cycle

Number of subjects in period 2[7]	MPR+R	MPR+p	MPp+p
Started	24	53	81
Completed	24	53	81

Notes:

[7] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The open label extension phase was optional.

Period 3

Period 3 title	Follow-up Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	MPR+R

Arm description:

Subjects in the follow-up phase were followed for overall survival and subsequent anti-myeloma treatment regimens until all subjects were followed for at least 5 years from randomization or had died.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	MPR+p

Arm description:

Subjects in the follow-up phase were followed for overall survival and subsequent anti-myeloma treatment regimens until all subjects were followed for at least 5 years from randomization or had died.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	MPp+p

Arm description:

Subjects in the follow-up phase were followed for overall survival and subsequent anti-myeloma

treatment regimens until all subjects were followed for at least 5 years from randomization or had died.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3[8]	MPR+R	MPR+p	MPp+p
Started	19	41	61
Completed	23	30	33
Not completed	88	91	87
Adverse event, serious fatal	77	85	82
Lost to follow-up	11	6	5
Joined	92	80	59
Induction-Maintance Period	92	80	59

Notes:

[8] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects from both the induction-maintenance phase and the OLEP were observed and monitored during the follow-up periods; therefore the number of subjects in each arm of the trial from both periods were reported in the follow-up phase and were greater than that in the OLEP.

Baseline characteristics

Reporting groups	
Reporting group title	Induction + Maintenance Phase: MPR+R
Reporting group description:	
During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg by mouth (PO) daily (QD) on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on Days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle for up to 9 cycles (MPR), followed by maintenance therapy with single-agent lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle from cycle 10 until progressive disease (PD). If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle at the discretion of the investigator.	
Reporting group title	Induction + Maintenance Phase: MPR+p
Reporting group description:	
During the double-blind induction phase, participants received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles, followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD. If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.	
Reporting group title	Induction + Maintenance Phase: MPp+p
Reporting group description:	
During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles (MPp), followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD. If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.	

Reporting group values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p
Number of subjects	152	153	154
Age Categorical Units: Subjects			
<=75 years	116	116	116
>75 years	36	37	38
Age Continuous Units: years			
arithmetic mean	72	72.1	72
standard deviation	± 5.33	± 5.2	± 5.26
Gender, Male/Female Units: Subjects			
Female	81	71	79
Male	71	82	75
Race/Ethnicity, Customized Units: Subjects			
White	151	151	151
Black	1	0	0
Hispanic	0	0	1
Asian / Pacific Islander	0	0	0

American Indian or Alaska Native	0	0	0
Other	0	2	2
International Staging System (ISS)			
The ISS divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Stage I: Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L); Stage II: Neither stage I or III, meaning that either the beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), or the albumin level is below 3.5 while the beta-2 microglobulin is less than 3.5 Stage III: Serum beta-2 microglobulin is greater than 5.5.			
Units: Subjects			
Stage I	28	32	28
Stage II	50	47	48
Stage III	74	74	78
Creatinine Clearance Units: Subjects			
>=60 ml/min	72	83	77
<60 ml/min	78	69	76
Missing	2	1	1
Beta2 Microglobulin Units: Subjects			
>5.5 mg/L	74	78	67
<=5.5 mg/L	77	75	87
Missing	1	0	0
Albumin Units: Subjects			
>35 g/L	87	82	81
<= 35 g/L	63	70	72
Missing	2	1	1
C-reactive Protein Units: Subjects			
>4 mg/L	64	56	64
<=4 mg/L	84	93	89
Missing	4	4	1
Multiple Myeloma Subtype Units: Subjects			
Immunoglobulin A (IgA)	39	38	33
Other	108	112	116
Missing	5	3	5
Karnofsky Performance Scale			
Karnofsky Performance Scale classifies patients according to their functional impairment. Scores range from 0-100, the lower the score, the greater the impairment and worse prospect of survival for most serious illnesses.			
Units: Subjects			
60 = needs occasional assistance; can care for self	13	16	11
70 = Cares for self;unable to do active work	40	20	22
80 = Normal activity with efforts; some symptoms	37	54	43
90 = able to carry on activities, minor complaints	40	40	51
100 = normal; no complaints	21	23	27
Missing	1	0	0

Study Specific Characteristic | Weight			
Units: kilograms			
arithmetic mean	73.5	72	72.1
standard deviation	± 14.77	± 12.79	± 15.2
Study Specific Characteristic | Height			
Units: centimeter			
arithmetic mean	164.8	165.3	165.7
standard deviation	± 9.81	± 9.33	± 9.79
Study Specific Characteristic | Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	133.9	135.3	136.4
standard deviation	± 17.71	± 18.49	± 20.13
Study Specific Characteristic | Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	78.5	77.2	78.8
standard deviation	± 9.53	± 10.08	± 10.4
Study Specific Characteristic | Temperature			
Units: degrees centigrade			
arithmetic mean	36.5	36.5	36.5
standard deviation	± 0.41	± 0.38	± 0.4
Study Specific Characteristic | Pulse			
Units: beats per minute			
arithmetic mean	76	77.3	76.3
standard deviation	± 9.77	± 10.5	± 10.8
Study Specific Characteristic | Plasma Cells in the Bone Marrow			
Units: percentage of plasma cells			
arithmetic mean	39.7	39.3	37.9
standard deviation	± 24.83	± 25.01	± 23.65

Reporting group values	Total		
Number of subjects	459		
Age Categorical			
Units: Subjects			
<=75 years	348		
>75 years	111		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	231		
Male	228		
Race/Ethnicity, Customized			
Units: Subjects			
White	453		
Black	1		
Hispanic	1		
Asian / Pacific Islander	0		

American Indian or Alaska Native	0		
Other	4		
International Staging System (ISS)			
The ISS divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Stage I: Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L); Stage II: Neither stage I or III, meaning that either the beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), or the albumin level is below 3.5 while the beta-2 microglobulin is less than 3.5 Stage III: Serum beta-2 microglobulin is greater than 5.5.			
Units: Subjects			
Stage I	88		
Stage II	145		
Stage III	226		
Creatinine Clearance Units: Subjects			
>=60 ml/min	232		
<60 ml/min	223		
Missing	4		
Beta2 Microglobulin Units: Subjects			
>5.5 mg/L	219		
<=5.5 mg/L	239		
Missing	1		
Albumin Units: Subjects			
>35 g/L	250		
<= 35 g/L	205		
Missing	4		
C-reactive Protein Units: Subjects			
>4 mg/L	184		
<=4 mg/L	266		
Missing	9		
Multiple Myeloma Subtype Units: Subjects			
Immunoglobulin A (IgA)	110		
Other	336		
Missing	13		
Karnofsky Performance Scale			
Karnofsky Performance Scale classifies patients according to their functional impairment. Scores range from 0-100, the lower the score, the greater the impairment and worse prospect of survival for most serious illnesses.			
Units: Subjects			
60 = needs occasional assistance; can care for self	40		
70 = Cares for self;unable to do active work	82		
80 = Normal activity with efforts; some symptoms	134		
90 = able to carry on activities, minor complaints	131		
100 = normal; no complaints	71		
Missing	1		

Study Specific Characteristic | Weight Units: kilograms arithmetic mean standard deviation	- -		
Study Specific Characteristic | Height Units: centimeter arithmetic mean standard deviation	- -		
Study Specific Characteristic | Systolic Blood Pressure Units: mmHg arithmetic mean standard deviation	- -		
Study Specific Characteristic | Diastolic Blood Pressure Units: mmHg arithmetic mean standard deviation	- -		
Study Specific Characteristic | Temperature Units: degrees centigrade arithmetic mean standard deviation	- -		
Study Specific Characteristic | Pulse Units: beats per minute arithmetic mean standard deviation	- -		
Study Specific Characteristic | Plasma Cells in the Bone Marrow Units: percentage of plasma cells arithmetic mean standard deviation	- -		

End points reporting groups

Reporting group title	Induction + Maintenance Phase: MPR+R

Reporting group description:

During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg by mouth (PO) daily (QD) on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on Days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle for up to 9 cycles (MPR), followed by maintenance therapy with single-agent lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle from cycle 10 until progressive disease (PD). If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Induction + Maintenance Phase: MPR+p

Reporting group description:

During the double-blind induction phase, participants received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles, followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD. If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Induction + Maintenance Phase: MPp+p

Reporting group description:

During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles (MPp), followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD. If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	MPR+R

Reporting group description:

Subjects who were treated with MPR+R and experienced PD during the induction or maintenance treatment periods were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	MPR+p

Reporting group description:

Subjects who were treated with MPR+p and experienced PD during the induction or maintenance treatment periods were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	MPp+p

Reporting group description:

Subjects who were treated with MPp+p and experienced PD during the induction or maintenance treatment periods were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	MPR+R

Reporting group description:

Subjects in the follow-up phase were followed for overall survival and subsequent anti-myeloma treatment regimens until all subjects were followed for at least 5 years from randomization or had died.

Reporting group title	MPR+p

Reporting group description:

Subjects in the follow-up phase were followed for overall survival and subsequent anti-myeloma treatment regimens until all subjects were followed for at least 5 years from randomization or had died.

Reporting group title	MPp+p

Reporting group description:

Subjects in the follow-up phase were followed for overall survival and subsequent anti-myeloma treatment regimens until all subjects were followed for at least 5 years from randomization or had died.

Primary: Kaplan Meier Estimates of Progression-free Survival (PFS) Based on the Response Assessment by the Central Adjudication Committee (CAC) and Food and Drug Administration (FDA) Censoring Rules

End point title	Kaplan Meier Estimates of Progression-free Survival (PFS) Based on the Response Assessment by the Central Adjudication Committee (CAC) and Food and Drug Administration (FDA) Censoring Rules

End point description:

PFS was calculated as the time from randomization to the earlier of the first documentation of progressive disease (PD) as determined by the CAC, or death on study due to any cause. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. Unblinding date. Intent to Treat (ITT) population was defined as all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Primary

End point timeframe:

From date of randomization to data cut-off of 11 May 2010; up to 39 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: months				
median (confidence interval 95%)	31.3 (19.84 to 99999)	14.1 (12.93 to 16.61)	12.9 (11.97 to 15.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

PFS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.388

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.274
upper limit	0.55

Notes:

[1] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

PFS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.494
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.344
upper limit	0.695

Notes:

[2] - Based on proportional hazard models comparing the functions associated with the treatment arms.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

PFS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.118 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.586
upper limit	1.064

Notes:

[3] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Primary: Kaplan Meier Estimates of Progression-free Survival Time (PFS) Based on

European Medicines Agency (EMA) Guidelines Based on the Response Assessment by the CAC

End point title	Kaplan Meier Estimates of Progression-free Survival Time (PFS) Based on European Medicines Agency (EMA) Guidelines Based on the Response Assessment by the CAC[4]

End point description:

PFS was calculated as the time from randomization to the earlier of the first documentation of progressive disease (PD) as determined by the CAC, or death on study due to any cause. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. Unblinding date. ITT population was defined as all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Primary

End point timeframe:

Date of randomization to data cut-off of 11 May 2010; up to 39 months

Notes:

[4] - 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: The primary endpoint compares MPR+R with MP+p and the reasons only two arms are reported. The study was not designed to compare MPR+P with MP+p.

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPp+p		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	154		
Units: months				
median (confidence interval 95%)	34.1 (25.69 to 99999)	15 (12.3 to 17.24)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.455
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.627

Notes:

[5] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Primary: Kaplan Meier Estimates of Progression-free Survival (PFS) from Start of

Maintenance Therapy Period Based on the Response Assessment by the Central Adjudication Committee (CAC)

End point title	Kaplan Meier Estimates of Progression-free Survival (PFS) from Start of Maintenance Therapy Period Based on the Response Assessment by the Central Adjudication Committee (CAC)[6]

End point description:

PFS calculated from the start of the Maintenance period to the earlier of the first documentation of progressive disease (PD) as determined by the CAC, or death on study due to any cause. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. ITT population of subjects in Arms MPR+R and MPR+p who entered maintenance within the double-blind treatment period

End point type	Primary

End point timeframe:

Approximately week 37 (start of cycle 10) to week 165; up to up to data cut-off of 11 May 2010

Notes:

[6] - 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: The primary endpoint compares MPR+R with MP+p and the reasons only two arms are reported. The study was not designed to compare MPR+P with MP+p.

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	94		
Units: weeks				
median (confidence interval 95%)	112 (83.29 to 99999)	32.3 (23.57 to 52.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.214
upper limit	0.541

Notes:

[7] - P-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Primary: Kaplan Meier Estimates of Progression-free Survival (PFS) from Start of Maintenance Therapy Period Based Investigator Assessment at a Later Cut-off date

of 30 April 2013

End point title	Kaplan Meier Estimates of Progression-free Survival (PFS) from Start of Maintenance Therapy Period Based Investigator Assessment at a Later Cut-off date of 30 April 2013[8]

End point description:

PFS calculated from the start of the Maintenance period to the earlier of the first documentation of progressive disease (PD) as determined by the CAC, or death on study due to any cause. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. ITT population of subjects in Arms MPR+R and MPR+p who entered maintenance within the double-blind treatment period

End point type	Primary

End point timeframe:

From date of randomization to data cut-off of 30 April 2013; up to 75 months

Notes:

[8] - 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: The primary endpoint and primary analysis of PFS compared MPR+R with MP+p and the statistical analysis was reported. The additional PFS data from start of maintenance therapy was analyzed by the investigators, but was not considered part of the primary analysis and rationale to the statistical analysis being reported between the MPR+R group and the MPR+p group.

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	94		
Units: months				
median (confidence interval 95%)	21.4 (16.58 to 35.72)	6.4 (4.64 to 9.08)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

PFS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.394
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.275
upper limit	0.564

Notes:

[9] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups

Primary: Kaplan Meier Estimates of PFS Time Based on the Investigator Response Assessment at a later cut off date

End point title	Kaplan Meier Estimates of PFS Time Based on the Investigator Response Assessment at a later cut off date

End point description:

PFS was calculated as the time from randomization to the earlier of the first documentation of progressive disease (PD) as determined by the investigator, or death on study due to any cause. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. ITT was defined as all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Primary

End point timeframe:

From February 2007 to May 2016; study duration of 111 months; date maximum treatment duration for MPR + R = 428 weeks, MPR + p = 162.7 weeks and MPp + P = 160.3 weeks

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: months				
median (confidence interval 95%)	27.4 (21.25 to 34.34)	14.3 (13.19 to 15.69)	13.7 (12.01 to 14.77)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

PFS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.373
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.276
upper limit	0.505

Notes:

[10] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

PFS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.482
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.354
upper limit	0.654

Notes:

[11] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Secondary: Kaplan Meier Estimates of Overall Survival (OS) Based on the Investigator Response Assessment

End point title	Kaplan Meier Estimates of Overall Survival (OS) Based on the Investigator Response Assessment

End point description:

OS was defined as the time between randomization and death. Subjects who died, regardless of the cause of death, were considered to have had an event. Subjects who were lost to follow-up prior to the end of the trial, or who were withdrawn from the trial, were censored at the time of last contact. Subjects who were still being treated were censored at the last available date available, or clinical cut-off date, if it was earlier. ITT population was defined as all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

From Feb 2007 to May 2016; study duration of 111 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: months				
median (confidence interval 95%)	55.9 (49.11 to 64.34)	53.1 (43.06 to 60.63)	53.9 (47.11 to 64.11)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

OS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.704 [12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.798
upper limit	1.396

Notes:

[12] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

OS was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.67 [13]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.714
upper limit	1.241

Notes:

[13] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Secondary: Kaplan Meier Estimates of Time to Progression (TTP) Based on Response Assessment by the Central Adjudication Committee (CAC)

End point title	Kaplan Meier Estimates of Time to Progression (TTP) Based on Response Assessment by the Central Adjudication Committee (CAC)

End point description:

TTP was the time between randomization and disease progression as determined by the CAC. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone

disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. ITT population was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

up to 165 weeks; up to 11 May 2010 cutoff

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: weeks				
median (confidence interval 95%)	148.1 (100 to 99999)	62.7 (57.14 to 74.14)	61.3 (52.29 to 70.14)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.337
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.231
upper limit	0.493

Notes:

[14] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.414

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.284
upper limit	0.603

Notes:

[15] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.826
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.606
upper limit	1.125

Notes:

[16] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Secondary: Kaplan Meier Estimates of Time to Progression (TTP) Based on the Investigator Assessment with a later cut-off date

End point title	Kaplan Meier Estimates of Time to Progression (TTP) Based on the Investigator Assessment with a later cut-off date

End point description:

TTP was the time between randomization and disease progression as determined by the investigator. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. ITT population was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Date of randomization to data cut-off of 30 April 2013; up to 75 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: months				
median (confidence interval 95%)	29.1 (22.53 to 39.51)	14.6 (13.39 to 16.18)	13.9 (12.73 to 14.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [17]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.325
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.235
upper limit	0.451

Notes:

[17] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.404
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	0.563

Notes:

[18] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.112 [19]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.802
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.054

Notes:

[19] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Secondary: Percentage of subjects in Disease Response Categories Representing Their Best Response During the Double-blind Treatment Period

End point title	Percentage of subjects in Disease Response Categories Representing Their Best Response During the Double-blind Treatment Period

End point description:

Best response was determined by the Central Assessment Committee (CAC) based on the European Group for Blood and Marrow Transplantation (EBMT) criteria: Complete Response (CR)-absence of serum and urine monoclonal paraprotein for 6 weeks, plus no increase in size or number of bone lesions, plus other factors); Partial Response (PR)-not all CR criteria, plus >=50% reduction in serum monoclonal paraprotein plus others; Stable Disease (SD)- not PR or PD; Progressive Disease (PD)- reappearance of monoclonal paraprotein, bone lesions, other; Not Evaluable (NE). ITT population was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Up to 165 weeks; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: percentage of participants				
number (not applicable)				
Complete response (CR)	9.9	3.3	3.2	
Partial response (PR)	67.1	64.7	46.8	
Stable disease (SD)	18.4	26.1	45.5	
Progressive disease (PD)	0	1.3	0	
Response not evaluable (NE)	4.6	4.6	4.5	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - P-value calculation excludes the category - Response not evaluable (NE)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - P-value calculation excludes the category - Response not evaluable (NE)

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - P-value calculation excludes the category - Response not evaluable (NE)

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Based on dichotomized response: 1) CR or PR 2) SD or PD or NE	
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.04
upper limit	5.47

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Based on dichotomized response: 1) CR or PR 2) SD or PD or NE	
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.62

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Based on dichotomized response: 1) CR or PR 2) SD or PD or NE	
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	3.37

Secondary: Percentage of Participants in Disease Response Categories Representing Their Best Response During the Treatment Period (Induction plus maintenance) based on the investigators assessment

End point title	Percentage of Participants in Disease Response Categories Representing Their Best Response During the Treatment Period (Induction plus maintenance) based on the investigators assessment

End point description:

Best response was determined by the Investigators based on the European Group for Blood and Marrow

Transplantation (EBMT) criteria: Complete Response (CR)-absence of serum and urine monoclonal paraprotein for 6 weeks, plus no increase in size or number of bone lesions, plus other factors); Partial Response (PR)-not all CR criteria, plus >=50% reduction in serum monoclonal paraprotein plus others; Stable Disease (SD)- not PR or PD; Progressive Disease (PD)- reappearance of monoclonal paraprotein, bone lesions, other; Not Evaluable (NE). ITT was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Response assessed every 28 days up to 3 years, then every 56 days; From date of first dose of study drug to 30 April 2013; up to 75 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: percentage of subjects				
number (not applicable)				
CR or PR	78.9	75.8	54.5	
CR	19.7	11.1	5.8	
PR	59.2	64.7	48.7	
SD	15.8	20.3	40.9	
PD	0	1.3	0	
Response not evaluable (NE)	5.3	2.6	4.5	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Dichotomized Response 1) CR or PR 2) SD or PD or NE	
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.89
upper limit	5.17

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Dichotomized Response 1) CR or PR 2) SD or PD or NE	
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.584
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.05

Statistical analysis title	Statistical Analysis 6
Statistical analysis description: Dichotomized Response 1) CR or PR 2) SD or PD or NE	
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	4.25

Secondary: Time to First Response

End point title	Time to First Response
End point description: Time to first response was defined as the time from the start of treatment until first response as assessed by the Central Assessment Committee (CAC) based on European Group for Blood and Marrow Transplantation (EBMT) criteria. Participants who had achieved at least a PR or CR at the time of the analysis.	
End point type	Secondary
End point timeframe: Response assessed every 28 days up to 3 years, then every 56 days; Up to 66 weeks; up to data cut-off of 11 May 2010	

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	104	77	
Units: weeks				
median (full range (min-max))	8.1 (3.9 to 38)	8.1 (3.7 to 28.1)	12.3 (4.1 to 66.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - Rank Sum Test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.607 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - Rank Sum Test

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - Rank Sum Test

Secondary: Time to First Response based On a later cut-off date

End point title	Time to First Response based On a later cut-off date

End point description:

Time to first response was defined as the time from randomization to the time when the response criteria for at least a PR was first met based on the investigators review. Participants who had achieved at least a PR or CR at the time of the analysis.

End point type	Secondary

End point timeframe:

Response assessed every 28 days up to 3 years, then every 56 days; From date of first dose of study drug to 30 April 2013; up to 75 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120	116	84	
Units: months				
median (full range (min-max))	2.8 (1.1 to 34.6)	2.7 (1 to 10.4)	3.7 (1.8 to 19.6)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - Rank Sum Test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.156 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - Rank Sum Test

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - Rank Sum Test

Secondary: Kaplan Meier Estimates for Duration of Response as Determined by the Central Adjudication Committee (CAC)

End point title	Kaplan Meier Estimates for Duration of Response as Determined by the Central Adjudication Committee (CAC)

End point description:

Duration of myeloma response was defined as the time from the initial response date to the earlier of

progressive disease (PD) as determined by the CAC or death on study. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. ITT population who achieved a PR or CR at the time of analysis.

End point type	Secondary

End point timeframe:

Up to 149 weeks; up to data cut-off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	104	77	
Units: weeks				
median (confidence interval 95%)	121.6 (96 to 99999)	56.1 (52.14 to 64.29)	55.4 (44.14 to 76.14)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Duration of Response (DOR) was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [29]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.348
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.228
upper limit	0.531

Notes:

[29] - The p-value is based on unstratified log rank test of Kaplan Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Duration of Response (DOR) was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.419
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.281
upper limit	0.623

Notes:

[30] - The p-value is based on unstratified log rank test of Kaplan Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Duration of Response (DOR) was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.302 [31]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.825
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.571
upper limit	1.191

Notes:

[31] - The p-value is based on unstratified log rank test of Kaplan Meier curve differences between the treatment groups.

Secondary: Kaplan Meier Estimates for Duration of Myeloma Response as determined by the investigators review with a later cut-off date

End point title	Kaplan Meier Estimates for Duration of Myeloma Response as determined by the investigators review with a later cut-off date

End point description:

Duration of myeloma response was defined as the time from the initial response date to the disease progression or death on study, whichever occurred first. PD was based on the European Group for Blood and Marrow Transplantation/International Bone Marrow Transplant Registry/Autologous Bone Marrow Transplant Registry [EBMT/IBMTR/ABMTR] criteria. PD criteria includes increasing monoclonal paraprotein levels, bone marrow findings, worsening lytic bone disease, progressively enlarging extramedullary plasmacytomas, or hypercalcemia. Includes participants who achieved at least a CR or PR. There were 2 participants in Arm MPR+R and 3 participants in Arm MPR+p who were assessed by investigators with a response to treatment (CR or PR) but who were excluded from the duration of response analysis because they had no measurable disease at baseline.

End point type	Secondary

End point timeframe:

Response assessed every 28 days up to 3 years, then every 56 days; From date of first dose of study

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118	113	84	
Units: months				
median (confidence interval 95%)	26.5 (19.41 to 35.76)	12.4 (11.18 to 13.85)	12 (9.47 to 14.54)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

DOR was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [32]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.259
upper limit	0.529

Notes:

[32] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

DOR was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [33]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.433

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.307
upper limit	0.612

Notes:

[33] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

DOR was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.344 [34]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.857
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.622
upper limit	1.181

Notes:

[34] - The p-value is based on unstratified log rank test of Kaplan-Meier curve differences between the treatment groups.

Secondary: Kaplan Meier Estimates for Time to Next Antimyeloma Therapy

End point title	Kaplan Meier Estimates for Time to Next Antimyeloma Therapy

End point description:

Time to the next antimyeloma therapy was defined as time from randomization to the start of another non-protocol antimyeloma therapy. Subjects who do not receive another anti-myeloma therapy were censored at the last assessment or follow-up visit known to have received no new therapy. ITT was defined as all participants who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Up to 75 months; 30 April 2013 cut-off

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: months				
median (confidence interval 95%)	28 (22.7 to 39.64)	15.2 (14.08 to 17.5)	15.3 (14.08 to 16.68)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Time to next anti-myeloma therapy was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [35]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.413
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.312
upper limit	0.547

Notes:

[35] - The p-value is based on unstratified log rank test of Kaplan Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Time to next anti-myeloma therapy was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [36]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.495
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.373
upper limit	0.656

Notes:

[36] - The p-value is based on unstratified log rank test of Kaplan Meier curve differences between the treatment groups.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Time to next anti-myeloma therapy was compared between treatment arms using the unstratified log-rank test. A Cox proportional hazards model was used to estimate relative risk hazard rate (risk) ratio along with 95% CIs.

Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174 [37]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.656
upper limit	1.08

Notes:

[37] - The p-value is based on unstratified log rank test of Kaplan Meier curve differences between the treatment groups.

Secondary: Number of Subjects with Adverse Events (AEs) During the Induction-Maintenance Period

End point title	Number of Subjects with Adverse Events (AEs) During the Induction-Maintenance Period

End point description:

A TEAE is as any AE occurring or worsening on or after the first treatment of any study drug, and within 30 days after the last dose of the last study drug. Severity grades according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE) on a 1-5 scale: Grade 1= Mild AE, Grade 2= Moderate AE, Grade 3= Severe AE, Grade 4= Life-threatening or disabling AE, Grade 5=Death related to AE. Dose reduction includes reduction with or without interruption. Safety population was defined as all randomized subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Time of first dose of study drug to 30 days after the last dose of study drug plus follow up period; maximum exposure to Lenalidomide/Placebo in MPR + R and and MPp+p = 190 days and MPR + p = 189 days; maximum exposure to Melphalan in any arm was 39 days.

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	152	153	
Units: subjects				
>=1 adverse event (AE)	150	151	153	
>=1 CTCAE grade 3-4 AE	139	131	107	
>=1 CTCAE grade 5 AE	11	8	7	
>=1 serious AE (SAE)	79	66	57	
>=1 AE related to Lenaldomide/Placebo	148	145	131	
>=1 AE related to Melphalan	140	134	126	
>=1AE related to Prednisone	88	94	94	

>=1 Grade 3-4 AE related to Lenaldomide/Placebo	132	118	67	
>=1 Grade 3-4 AE related to Melphalan	118	110	61	
>=1 Grade 3-4 AE related to Prednisone	33	29	21	
>=1 Grade 5 AE related to Lenalidomide/Placebo	4	2	2	
>=1 Grade 5 AE related to Melphalan	4	1	3	
>=1 Grade 5 AE related to Prednisone	1	1	1	
>=1 SAE related to Lenalidomide/Placebo	43	34	10	
>=1 SAE related to Melphalan	30	24	11	
>=1 SAE related to Prednisone	20	16	5	
>=1 AE leading to Lenalidomide/Placebo withdrawal	40	26	14	
>=1 AE leading to Melphalan withdrawal	20	20	10	
>=1 AE leading to Prednisone withdrawal	19	20	10	
>=1 AE leading to Lenalidomide/Plac dose reduction	76	70	26	
>=1 AE leading to Melphalan dose reduction	46	59	21	
>=1 AE leading to Prednisone dose reduction	13	7	6	
>=1 AE leading to Lenalidomide/Plac dose interrupt	99	85	52	
>=1 AE leading to Melphalan dose interruption	5	2	0	
>=1 AE leading to Prednisone dose interruption	25	38	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with AEs During the Open-Label Extension Phase (OLEP)

End point title	Number of Subjects with AEs During the Open-Label Extension Phase (OLEP)

End point description:

A TEAE is as any AE occurring or worsening on or after the first treatment of any study drug, and within 30 days after the last dose of the last study drug. Severity grades according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE) on a 1-5 scale: Grade 1= Mild AE, Grade 2= Moderate AE, Grade 3= Severe AE, Grade 4= Life-threatening or disabling AE, Grade 5=Death related to AE. Dose reduction includes reduction with or without interruption. A serious AE is any AE occurring at any dose that: • Results in death; • Is life-threatening; • Requires or prolongs existing inpatient hospitalization; • Results in persistent or significant disability/incapacity; • Is a congenital anomaly/birth defect; • Constitutes an important medical event. Safety population was defined as all randomized subjects who received at least one dose of study treatment

End point type	Secondary

End point timeframe:

Time of first dose of study drug during the OLEP up to 30 days after the last dose of study drug; maximum exposure to Lenalidomide was 1239 days

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	53	80	
Units: Subjects				
>=1 adverse event (AE)	23	50	78	
>=1 CTCAE grade 3-4 AE	18	40	73	
>=1 CTCAE grade 5 AE	2	10	7	
>=1 serious AE (SAE)	11	21	39	
>=1 AE related to Lenalidomide	20	47	72	
>=1 Grade 3-4 AE related to Lenalidomide	14	37	64	
>=1 Grade 5 AE related to Lenalidomide	0	0	3	
>=1 SAE related to Lenalidomide	7	5	13	
>=1 AE leading to Lenalidomide withdrawal	3	9	14	
>=1 AE leading to Lenalidomide dose reduction	8	14	20	
>=1 AE leading to Lenalidomide dose interrupt	14	36	51	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer (EORTC QLQ-C30) Global Quality of Life Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer (EORTC QLQ-C30) Global Quality of Life Scale

End point description:

EORTC QLC-C30 is a 30-item questionnaire to assess the quality of life in cancer patients. EORTC QLQ-C30 includes functional scales (physical, role, cognitive, emotional, social), global health status, symptom scales (fatigue, pain, nausea/vomiting), and other (dyspnoea, appetite loss, insomnia, constipation/diarrhea, financial difficulties). Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); two used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; where a higher score indicates a better quality of life. Data up to cycle 19 are presented due to small sample of subjects after cycle 19. ITT population was defined as all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16 and 19; Up to 30 April 2013 data cut-off

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=111,119,124)	1.9 (± 26.27)	6.3 (± 18.29)	6.1 (± 19.48)	
Cycle 7 - approximately Month 7 (n=96,108,109)	8.3 (± 25.07)	7.7 (± 22.97)	4.3 (± 24)	
Cycle 10 -approximately Month 10 (n=85,87,97)	12.2 (± 25.08)	8.5 (± 24.77)	6 (± 24.52)	
Cycle 13 - approximately Month 13 (n=70,70,79)	8.6 (± 28.05)	8.7 (± 24.09)	5.3 (± 22.41)	
Cycle 16 approximately Month 16 (n=61,51,63)	11.1 (± 24.89)	7.7 (± 26.07)	7.9 (± 25.81)	
Cycle 19 approximately Month 16 (n=50,36,43)	5.2 (± 24.73)	8.8 (± 25.58)	8.1 (± 23.67)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.1589 [39]
Method	t-test, 2-sided

Notes:

[38] - P-values reported from change from baseline at cycle 4 only

[39] - The p-value is calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.1379 [41]
Method	t-test, 2-sided

Notes:

[40] - P-values reported from change from baseline at cycle 4 only

[41] - The p-value is calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.9399 [43]
Method	t-test, 2-sided

Notes:

[42] - P-values reported from change from baseline at cycle 4 only

[43] - The p-value is calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Physical Functioning Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Physical Functioning Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged and transformed to a 0-100 scale where a higher score indicates a better level of physical functioning. Data up to cycle 19 are presented due to small sample of participants after cycle 19. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16 and 19; Up to 30 April 2013 data cut-off

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	125	129	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=117,125,129)	2 (± 23.78)	3.9 (± 20.24)	4.6 (± 18.75)	
Cycle 7 - approximately Month 7 (n= 100, 112,111)	8.4 (± 22.85)	7.5 (± 22.37)	3.7 (± 22.02)	
Cycle 10 - approximately Month 10 (n = 89,96,96)	8.3 (± 22.83)	8.4 (± 25.52)	5.1 (± 20.42)	
Cycle 13 - approximately Month 13 (n=75, 74, 80)	9 (± 23.71)	9.6 (± 25.41)	3.1 (± 19.75)	
Cycle 16 - approximately Month 16 (n=64, 54, 65)	10.3 (± 24.99)	8.6 (± 23.27)	0.7 (± 20.6)	
Cycle 19 - approximately Month 19 (n= 53,39,43)	9.9 (± 21.42)	7.6 (± 22.91)	7.2 (± 19.65)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.3372 [45]
Method	t-test, 2-sided

Notes:

[44] - P-values reported from change from baseline at cycle 4 only

[45] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.482 [47]
Method	t-test, 2-sided

Notes:

[46] - P-values reported from change from baseline at cycle 4 only

[47] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.8006 [49]
Method	t-test, 2-sided

Notes:

[48] - P-values reported from change from baseline at cycle 4 only

[49] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Role Functioning Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Role Functioning Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to 0-100 scale; a higher score indicates a higher level of role functioning. Data reported up to cycle 16 on role functioning scale. ITT population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13 and 16; up to data cutoff of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=119,127,130)	1.8 (± 33.18)	3 (± 30.75)	7.4 (± 26.34)	
Cycle 7 - approximately Month 7 (n=99,112,113)	5.7 (± 35.57)	8 (± 32.42)	6.9 (± 31.16)	
Cycle 10 - approximately Month 10 (n=86,95,95)	9.3 (± 35.76)	7.5 (± 36.29)	5.6 (± 31.29)	
Cycle 13 - approximately Month 13 (n=74,74,82)	9.7 (± 40.36)	11.7 (± 33.42)	5.7 (± 30.68)	
Cycle 16 - approximately Month 16 (n=64,53,63)	12.2 (± 40.09)	8.5 (± 34.22)	7.1 (± 31.93)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.1391 [51]
Method	t-test, 2-sided

Notes:

[50] - P-value provided at Cycle 4 only.

[51] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.7702 [53]
Method	t-test, 2-sided

Notes:

[52] - P-value provided at Cycle 4 only.

[53] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.2167 [55]
Method	t-test, 2-sided

Notes:

[54] - P-value reported at Cycle 4 only

[55] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Emotional Functioning Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Emotional Functioning Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged and transformed to 0-100 scale; a higher score indicates a higher level of emotional functioning. Data reported up to cycle 16 on emotional functioning scale. ITT Population

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=115,125,128)	4.8 (± 25)	2.7 (± 22.59)	6.8 (± 18.75)	
Cycle 7 - approximately Month 7 (n=98,111,112)	8.8 (± 24.94)	4.2 (± 20.38)	5 (± 21.56)	
Cycle 10 - approximately Month 10 (n=86,92,97)	9 (± 23.28)	1.6 (± 22.07)	4.7 (± 22.05)	
Cycle 13 - approximately Month 13 (n=73,73,83)	8.2 (± 24.59)	1.1 (± 21.78)	6.6 (± 21.78)	
Cycle 16 - approximately Month 16 (n=63,52,63)	9.9 (± 23.23)	-0.2 (± 21.57)	6.9 (± 19.72)	

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.4649 [57]
Method	t-test, 2-sided

Notes:

[56] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[57] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.5118 [59]
Method	t-test, 2-sided

Notes:

[58] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[59] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.1188 [61]
Method	t-test, 2-sided

Notes:

[60] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[61] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Cognitive Functioning Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Cognitive Functioning Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to 0-100 scale; higher score indicates a higher level of cognitive functioning. Data reported up to cycle 16 on cognitive functioning scale. ITT population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; Up to data cut-off 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=115,125,128)	0.3 (± 21.51)	-2 (± 21.33)	1.3 (± 16.68)	
Cycle 7 - approximately Month 7 (n=98,111,113)	2.9 (± 22.31)	0.1 (± 17.33)	0.7 (± 18.42)	
Cycle 10 - approximately Month 10 (n=87,92,97)	1 (± 22.64)	-4.4 (± 19.89)	-2.7 (± 20.65)	
Cycle 13 - approximately Month 13 (n=73,73,83)	0 (± 21.34)	-3 (± 23.78)	-1.4 (± 17.69)	
Cycle 16 - approximately Month 16 (n=63,52,63)	0.3 (± 22.29)	-3.5 (± 27.48)	-4 (± 18.13)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.6798 [63]
Method	t-test, 2-sided

Notes:

[62] - P-values reported from change from baseline at cycle 4 only

[63] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.4081 [65]
Method	t-test, 2-sided

Notes:

[64] - P-values reported from change from baseline at cycle 4 only

[65] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.17 [67]
Method	t-test, 2-sided

Notes:

[66] - P-value provided only at Cycle 4

[67] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Fatigue Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Fatigue Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score indicates a higher level of fatigue. Data up to cycle 19 are presented due to small sample of participants after cycle 19.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Cycles 4, 7, 10, 13, 16 and 19; up to data cut-off 30 April 2013

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	125	128	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=117,125,128)	-3 (± 25.65)	-5.8 (± 24.1)	-5.1 (± 24.42)	
Cycle 7 - approximately Month 7 (n=100,112,109)	-8.1 (± 23.06)	-9.2 (± 26.23)	-6.4 (± 26.97)	
Cycle 10 - approximately Month 10 (n = 88, 86, 95)	-6.7 (± 27.47)	-7.4 (± 29.6)	-6.9 (± 28.5)	
Cycle 13 - approximately Month 13 (n= 74, 74, 79)	-7.7 (± 25.65)	-11.2 (± 29.91)	-7.3 (± 27.64)	
Cycle 16 - approximately Month 16 (n = 64, 54, 64)	-10.2 (± 26.83)	-10.5 (± 28.85)	-4.3 (± 25.64)	
Cycle 19 - approximately Month 19 (n = 53, 39, 42)	-8.5 (± 29.72)	-5.4 (± 30.8)	-9.3 (± 27.85)	

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.5146 [69]
Method	t-test, 2-sided

Notes:

[68] - P-values reported from change from baseline at cycle 4 only

[69] - The p-value was calculated based on a pooled t-test comparing two treatment groups.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.3839 [71]
Method	t-test, 2-sided

Notes:

[70] - P-values reported from change from baseline at cycle 4 only

[71] - The p-value was calculated based on a pooled t-test comparing two treatment groups.

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.8192 [73]
Method	t-test, 2-sided

Notes:

[72] - P-values reported from change from baseline at cycle 4 only

[73] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Nausea and Vomiting Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Nausea and Vomiting Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score indicates a higher level of nausea and vomiting. Data reported up to cycle 16 on nausea/vomiting scale. ITT population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=120,127,130)	3.3 (± 19.4)	-1.3 (± 17.14)	0 (± 17.36)	
Cycle 7 - approximately Month 7 (n=99,112,112)	0.5 (± 14.57)	-0.7 (± 19.94)	0.7 (± 14.73)	
Cycle 10 - approximately Month 10 (n=87,95,97)	1.9 (± 16.75)	-1.4 (± 19.4)	0.3 (± 14.23)	
Cycle 13 - approximately Month 13 (n=75,72,83)	0.7 (± 13.55)	-3 (± 19.65)	-0.4 (± 12.48)	
Cycle 16 - approximately Month 16 (n=64,52,62)	1 (± 12.9)	-4.2 (± 18.65)	-1.3 (± 9.21)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	= 0.1525 [75]
Method	t-test, 2-sided

Notes:

[74] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[75] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.0467 [77]
Method	t-test, 2-sided

Notes:

[76] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[77] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.5428 [79]
Method	t-test, 2-sided

Notes:

[78] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[79] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Pain Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Pain Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score indicates a higher level of pain. Data up to cycle 19 are presented due to small sample of participants after cycle 19. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13,16 and 19; up to data cut off 30 April 2013

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	125	128	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n= 117, 125, 128)	-13.8 (± 32.77)	-13.9 (± 33.72)	-13.3 (± 29.38)	
Cycle 7 - approximately Month 7 (n=100, 112, 112)	-18.3 (± 36.04)	-17.9 (± 31.38)	-11.9 (± 33.37)	
Cycle 10 - approximately Month 10 (n=89, 96, 98)	-17.2 (± 35.13)	-14.1 (± 37.33)	-8.7 (± 31.68)	
Cycle 13 - approximately Month 13 (n=74, 74, 80)	-14.4 (± 40.1)	-14.9 (± 33.28)	-12.3 (± 27.4)	
Cycle 16 - approximately Month 16 (n=64, 54, 65)	-21.6 (± 32.75)	-11.1 (± 32.69)	-12.8 (± 30.87)	
Cycle 19 - approximately Month 19 (n=53, 39, 43)	-19.2 (± 33.87)	-13.3 (± 36.71)	-17.8 (± 33.22)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.8932 [81]
Method	t-test, 2-sided

Notes:

[80] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[81] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	= 0.8838 [83]
Method	t-test, 2-sided

Notes:

[82] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[83] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 0.9911
Method	t-test, 2-sided

Notes:

[84] - P-value included at Cycle 4 (Change from Cycle 4 reported)

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Dyspnoea Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Dyspnoea Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to 0-100 scale; a higher score indicates a higher level of dyspnoea. Data reported up to cycle 16 on dyspnoea scale. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; Data as of 11 May 2010 cutoff

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=117,126,126)	-2.6 (± 29.74)	-6.4 (± 32.04)	0 (± 23.48)	
Cycle 7 - approximately Month 7 (n=100,110,110)	-1.7 (± 28.18)	-8.5 (± 32.07)	2.1 (± 20.82)	
Cycle 10 - approximately Month 10 (n=86,93,96)	-4.3 (± 30.6)	-4.3 (± 35.87)	3.8 (± 25.07)	
Cycle 13 - approximately Month 13 (n=73,73,81)	-5 (± 30.26)	-2.3 (± 30.6)	0 (± 22.35)	
Cycle 16 - approximately Month 16 (n=62,53,62)	-3.2 (± 29.39)	-6.3 (± 32.07)	1.6 (± 22.92)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[85]
P-value	= 0.4556 [86]
Method	t-test, 2-sided

Notes:

[85] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[86] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[87]
P-value	= 0.3411 [88]
Method	t-test, 2-sided

Notes:

[87] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[88] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[89]
P-value	= 0.0739 [90]
Method	t-test, 2-sided

Notes:

[89] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[90] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Insomnia Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Insomnia Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score for a symptom scale like the insomnia scale indicates a higher level of insomnia. Data reported up to cycle 16 on insomnia scale. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; Data as of 11 May 2010 cutoff

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=118,124,128)	2 (± 33.56)	-1.6 (± 31.77)	-5 (± 27.77)	
Cycle 7 - approximately Month 7 (n=100,109,111)	-1 (± 29.76)	-6.4 (± 27.02)	-5.7 (± 32.06)	
Cycle 10 - approximately Month 10 (n=87,94,96)	-5 (± 28.99)	-2.5 (± 25.04)	-1.7 (± 32.58)	
Cycle 13 - approximately Month 13 (n=75,73,83)	-4.9 (± 29.86)	0.9 (± 29.38)	-6.8 (± 29.8)	
Cycle 16 - approximately Month 16 (n=64,53,63)	-4.7 (± 32.46)	-0.6 (± 32.36)	-3.7 (± 31.18)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[91]
P-value	= 0.078 [92]
Method	t-test, 2-sided

Notes:

[91] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[92] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[93]
P-value	= 0.3933 [94]
Method	t-test, 2-sided

Notes:

[93] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[94] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[95]
P-value	= 0.3749 [96]
Method	t-test, 2-sided

Notes:

[95] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[96] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Appetite Loss Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Appetite Loss Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score for a symptom scale like the appetite loss scale indicates a higher level of appetite loss. Data reported up to cycle 16 on appetite loss scale. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=119,125,130)	1.7 (± 36.54)	1.9 (± 34.73)	-5.6 (± 25.96)	
Cycle 7 - approximately Month 7 (n=99,111,111)	-3.7 (± 33.64)	-5.7 (± 31.75)	-5.7 (± 27.66)	
Cycle 10 - approximately Month 10 (n=87,93,96)	-5 (± 33.15)	-5.4 (± 29.2)	-8 (± 29.32)	
Cycle 13 - approximately Month 13 (n=75,72,83)	-6.2 (± 36.23)	-8.8 (± 30.13)	-4.8 (± 32.15)	
Cycle 16 - approximately Month 16 (n=64,52,63)	-7.8 (± 36.01)	-16 (± 35.24)	-6.4 (± 28.62)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[97]
P-value	= 0.0678 [98]
Method	t-test, 2-sided

Notes:

[97] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[98] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[99]
P-value	= 0.9674 [100]
Method	t-test, 2-sided

Notes:

[99] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[100] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[101]
P-value	= 0.0511 [102]
Method	t-test, 2-sided

Notes:

[101] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[102] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Constipation Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Constipation Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to 0-100 scale; a higher score for a symptom scale like the constipation scale indicates a higher level of constipation. Data reported up to cycle 16 on constipation scale. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=114,124,128)	-1.8 (± 34.31)	4.8 (± 30.86)	-4.9 (± 27.45)	
Cycle 7 - approximately Month 7 (n=96,111,112)	-3.5 (± 36.35)	0.6 (± 30.14)	-2.7 (± 31.05)	
Cycle 10 - approximately Month 10 (n=86,93,97)	-5 (± 34.88)	-1.1 (± 28.43)	-1.7 (± 26.95)	
Cycle 13 - approximately Month 13 (n=73,73,81)	-5 (± 31.27)	-2.7 (± 28.74)	-3.3 (± 29.16)	
Cycle 16 - approximately Month 16 (n=63,51,62)	-1.6 (± 31.36)	-5.2 (± 30.82)	-2.2 (± 32.44)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[103]
P-value	= 0.4226 [104]
Method	t-test, 2-sided

Notes:

[103] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[104] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[105]
P-value	= 0.1198 [106]
Method	t-test, 2-sided

Notes:

[105] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[106] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[107]
P-value	= 0.0083 [108]
Method	t-test, 2-sided

Notes:

[107] - P-value included at Cycle 4 (Change from Cycle 4 reported):

[108] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Diarrhoea Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Diarrhoea Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score for a symptom scale like the diarrhea scale indicates a higher level of diarrhea. Data reported up to cycle 16 on diarrhea scale. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=115,125,124)	2.3 (± 28.85)	1.9 (± 24.06)	3.2 (± 25.65)	
Cycle 7 - approximately Month 7 (n=98,109,112)	3.4 (± 25.54)	-1.2 (± 23.09)	0.9 (± 22.13)	
Cycle 10 - approximately Month 10 (n=87,92,95)	1.1 (± 22.98)	1.4 (± 20.91)	0 (± 21.19)	
Cycle 13 - approximately Month 13 (n=73,73,80)	5.5 (± 30.43)	-1.4 (± 18.78)	0.8 (± 18.35)	
Cycle 16 - approximately Month 16 (n=63,52,61)	10.6 (± 35.83)	1.3 (± 19.75)	0.5 (± 17.74)	

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[109]
P-value	= 0.7984 [110]
Method	t-test, 2-sided

Notes:

[109] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[110] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[111]
P-value	= 0.8936 [112]
Method	t-test, 2-sided

Notes:

[111] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[112] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[113]
P-value	= 0.6665 [114]
Method	t-test, 2-sided

Notes:

[113] - P-value included at Cycle 4 (Change from Cycle 4 reported):

[114] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Financial Difficulties Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Patients With Cancer (EORTC QLQ-C30) Financial Difficulties Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer patients. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged, and transformed to a 0-100 scale; a higher score for a problem scale like the financial problems scale indicates a higher level of financial problems. Data reported up to cycle 16 on financial problems scale.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=111,123,125)	2.4 (± 24.91)	-1.1 (± 19.06)	-2.9 (± 18.93)	
Cycle 7 - approximately Month 7 (n=94,111,112)	2.1 (± 23.85)	-0.6 (± 28.07)	-2.1 (± 22.5)	
Cycle 10 - approximately Month 10 (n=84,92,97)	6 (± 21.44)	0.7 (± 28.81)	-1.7 (± 19.47)	
Cycle 13 - approximately Month 13 (n=70,72,83)	4.8 (± 21.45)	-0.5 (± 28.8)	-4 (± 26.75)	
Cycle 16 - approximately Month 16 (n=61,52,63)	1.6 (± 20.58)	-0.6 (± 35.24)	-5.3 (± 30.06)	

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[115]
P-value	= 0.0636 [116]
Method	t-test, 2-sided

Notes:

[115] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[116] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[117]
P-value	= 0.228 [118]
Method	t-test, 2-sided

Notes:

[117] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[118] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[119]
P-value	= 0.4443 [120]
Method	t-test, 2-sided

Notes:

[119] - P-value included at Cycle 4 (Change from Cycle 4 reported):

[120] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 and 19 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms Scale

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in patients with multiple myeloma. EORTC QLQ-MY20 includes four scales: disease symptoms, treatment side-effects, future perspective, and body image. Questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'). Scores were averaged, and transformed to a 0-100 scale; a higher score indicates more severe disease symptom(s). Data up to cycle 19 are presented due to small sample of participants after cycle 19. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16 and 19; up to data cut off of 30 April 2013

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	119	126	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=110, 119, 126)	-8.4 (± 19.53)	-8.8 (± 19.23)	-5.5 (± 15.79)	
Cycle 7 - approximately Month 7 (n=96, 109, 111)	-9.4 (± 20.94)	-10.4 (± 22.38)	-6.2 (± 20.82)	
Cycle 10 - approximately Month 10 (n=86, 92,96)	-8.5 (± 22.44)	-6 (± 24.47)	-4.6 (± 19.57)	
Cycle 13 - approximately Month 13 (n=72, 73, 79)	-7.1 (± 25.89)	-8.9 (± 25.12)	-6.5 (± 21.58)	
Cycle 16 - approximately Month 16 (n=62, 52, 63)	-10.6 (± 23.69)	-6.9 (± 25.92)	-3.8 (± 20.63)	
Cycle 19 - approximately Month 19 (n=51, 37, 43)	-12.4 (± 23.9)	-7.3 (± 28.46)	-3.8 (± 23.58)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority[121]
P-value	= 0.2007 [122]
Method	t-test, 2-sided

Notes:

[121] - P-values reported from change from baseline at cycle 4 only

[122] - The p-value was calculated based on a pooled t-test comparing two treatment groups.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority[123]
P-value	= 0.903 [124]
Method	t-test, 2-sided

Notes:

[123] - P-values reported from change from baseline at cycle 4 only

[124] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	245
Analysis specification	Pre-specified
Analysis type	superiority[125]
P-value	= 0.1468 [126]
Method	t-test, 2-sided

Notes:

[125] - P-values reported from change from baseline at cycle 4 only

[126] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) In Side Effects of Treatment Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) In Side Effects of Treatment Scale

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in patients with multiple myeloma. Questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'). Scores were averaged, and transformed to a 0-100 scale; a higher score represents a more severe overall side effect of treatment. Data up to cycle 19 are presented due to small sample of participants after cycle 19. ITT Population

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; Up to data cut-off of 30 April 2013

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	110	118	124	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=110, 118, 124)	1.1 (± 13.32)	-0.1 (± 13.26)	0.4 (± 12.52)	
Cycle 7 - approximately Month 7 (n=95, 108, 110)	0.5 (± 15.34)	-1.2 (± 14.1)	1.8 (± 13)	
Cycle 10 - approximately Month 10 (n=86, 90, 95)	-1.7 (± 14.22)	-0.1 (± 16.2)	0.9 (± 13.3)	
Cycle 13 - approximately Month 13 (n=72, 72, 78)	-3.9 (± 15.53)	-1.4 (± 14.69)	0.3 (± 12.78)	
Cycle 16 - approximately Month 16 (n=62, 51, 62)	-2.3 (± 14.62)	-2.7 (± 14.01)	-1.3 (± 11.19)	
Cycle 19 - approximately Month 19 (n=51, 36, 42)	-3.2 (± 14.84)	-0.6 (± 15.16)	-0.3 (± 15.55)	

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority[127]
P-value	= 0.6977 [128]
Method	t-test, 2-sided

Notes:

[127] - P-values reported from change from baseline at cycle 4 only

[128] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority[129]
P-value	= 0.5072 [130]
Method	t-test, 2-sided

Notes:

[129] - P-values reported from change from baseline at cycle 4 only

[130] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[131]
P-value	= 0.7572 [132]
Method	t-test, 2-sided

Notes:

[131] - P-values reported from change from baseline at cycle 4 only

[132] - The p-value was calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) In Future Perspective Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) In Future Perspective Scale

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in patients with multiple myeloma. Questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'). Scores were averaged, and transformed to a 0-100 scale. For the future perspective scale, a higher score indicates a better perspective of the future. Data reported up to cycle 16 for the future perspective scale. ITT Population.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=112,121,124)	4.7 (± 23.74)	4.3 (± 23.56)	7.6 (± 22.38)	
Cycle 7 - approximately Month 7 (n=93,108,112)	14.6 (± 24.45)	7.7 (± 23.86)	9.8 (± 20.62)	
Cycle 10 - approximately Month 10 (n=83,88,97)	17.3 (± 27.84)	6.6 (± 22.4)	14.5 (± 21.73)	
Cycle 13 - approximately Month 13 (n=71,73,81)	17.3 (± 27.15)	6.3 (± 23.78)	11.9 (± 24.67)	
Cycle 16 - approximately Month 16 (n=62,52,62)	18.5 (± 25.3)	7.7 (± 28.49)	14.4 (± 26.62)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[133]
P-value	= 0.3351 [134]
Method	t-test, 2-sided

Notes:

[133] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[134] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[135]
P-value	= 0.8982 [136]
Method	t-test, 2-sided

Notes:

[135] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[136] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[137]
P-value	= 0.2624 [138]
Method	t-test, 2-sided

Notes:

[137] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[138] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Change From Baseline to Cycles 4, 7, 10, 13, 16 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) In Body Image Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13, 16 in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) In Body Image Scale

End point description:

EORTC QLQ-MY20 is a validated questionnaire to assess the overall quality of life in patients with multiple myeloma. Questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'). Scores were averaged, and transformed to a 0-100 scale. For the body image scale, a higher score indicates a better body image. Data presented up to cycle 16 for body image scale. ITT Population

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13, 16; up to data cut off of 11 May 2010

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=110,117,119)	2.1 (± 35.36)	-0.3 (± 37.27)	4.5 (± 25.65)	
Cycle 7 - approximately Month 7 (n=88,104,108)	3.8 (± 33.32)	2.6 (± 37.94)	5.2 (± 27.78)	
Cycle 10 - approximately Month 10 (n=79,83,94)	7.6 (± 33.32)	-4 (± 43.69)	3.9 (± 26.72)	
Cycle 13 - approximately Month 13 (n=68,72,79)	1 (± 31.01)	-0.5 (± 44.23)	5.1 (± 32.51)	
Cycle 16 - approximately Month 16 (n=59,52,61)	3.4 (± 32.58)	6.4 (± 41.25)	2.7 (± 28.08)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority[139]
P-value	= 0.5618 [140]
Method	t-test, 2-sided

Notes:

[139] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[140] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPR+p
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority[141]
P-value	= 0.6189 [142]
Method	t-test, 2-sided

Notes:

[141] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[142] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority[143]
P-value	= 0.2532 [144]
Method	t-test, 2-sided

Notes:

[143] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[144] - P-value calculated based on a pooled t-test comparing two treatment groups

Secondary: Percentage of participants who received anti-myeloma salvage therapy at the time of progressive disease

End point title	Percentage of participants who received anti-myeloma salvage therapy at the time of progressive disease

End point description:

Anti-myeloma therapies administered during the course of the study included bortezomib, glucocorticoids, lenalidomide, thalidomide, alkylating agents and other antineoplastic agents.

End point type	Secondary

End point timeframe:

Following first line therapy including OLEP treatment up to final cut-off date of 17 May 2016; 111 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152	153	154	
Units: percentage of subjects				
number (not applicable)	57.9	81.7	83.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Subjects with Cancer (EORTC QLQ-C30) Social Functioning Scale

End point title	Change From Baseline to Cycles 4, 7, 10, 13 and 16 in European Organization for Research and Treatment of Cancer Questionnaire for Subjects with Cancer (EORTC QLQ-C30) Social Functioning Scale

End point description:

EORTC QLQ-C30 is a 30-item questionnaire to assess the overall quality of life in cancer subjects. Most questions used a 4-point scale (from 1 'Not at All' to 4 'Very Much'); 2 questions used a 7-point scale (from 1 'Very Poor' to 7 'Excellent'). Scores were averaged and transformed to a 0-100 scale, with a higher score indicating a better level of social functioning.

End point type	Secondary

End point timeframe:

Baseline (Day 0), Months 4, 7, 10, 13 and 16

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115	115	127	
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 4 - approximately Month 4 (n=115, 125, 127)	5.1 (± 35.05)	0.3 (± 26.6)	6 (± 22.78)	
Cycle 7 - approximately Month 7 (n=98, 111, 112)	8.3 (± 33.87)	4.4 (± 24.48)	6.1 (± 26.57)	
Cycle 10 - approximately Month 10 (n=87, 92, 97)	10.9 (± 34.27)	4.5 (± 29.87)	4.1 (± 27.22)	
Cycle 13 - approximately Month 13 (n=72, 73, 83)	11.8 (± 32.91)	7.5 (± 29.8)	6.2 (± 27.63)	
Cycle 16 - approximately Month 16 (n=63, 52, 63)	13.2 (± 33.35)	6.1 (± 30.79)	9.8 (± 28.66)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Induction + Maintenance Phase: MPR+R v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[145]
P-value	= 0.798 [146]
Method	t-test, 2-sided

Notes:

[145] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[146] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 2
Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPR+R
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority[147]
P-value	= 0.2305 [148]
Method	t-test, 2-sided

Notes:

[147] - P-value included at Cycle 4 (Change from Cycle 4 reported)

[148] - P-value calculated based on a pooled t-test comparing two treatment groups

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

P-value included at Cycle 4 (Change from Cycle 4 reported)

Comparison groups	Induction + Maintenance Phase: MPR+p v Induction + Maintenance Phase: MPp+p
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority[149]
P-value	= 0.0654
Method	t-test, 2-sided

Notes:

[149] - P-value calculated based on a pooled t-test comparing two treatment groups

Other pre-specified: Percentage of participants with second primary malignancies during the entire course of the trial

End point title	Percentage of participants with second primary malignancies during the entire course of the trial

End point description:

Second primary malignancies were monitored as events of interest and reported as serious adverse events throughout the course of the trial. Safety population includes participants who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

Date of first dose of study drug through the end of the follow-up period; up to 111 months

End point values	Induction + Maintenance Phase: MPR+R	Induction + Maintenance Phase: MPR+p	Induction + Maintenance Phase: MPp+p	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	152	153	
Units: Percentage of subjects				
number (not applicable)				
Hematologic malignancies	6	5.3	1.3	
Solid tumors	4.7	7.9	2.6	
Invasive second primary malignancies	10.7	12.5	3.9	
Non-invasive second primary malignancies	3.3	3.9	5.2	

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through to 30 days after the last dose

Adverse event reporting additional description:

During the induction-maintenance period there was a maximum exposure to Lenalidomide/Placebo in MPR + R and MPp+p = 190 days and MPR + p = 189 days; maximum exposure to Melphalan in any arm was 39 days.

During the OLEP period there was a maximum exposure to Lenalidomide was 1239 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Induction + Maintenance MPR+R

Reporting group description:

During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg by mouth (PO) daily (QD) on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on Days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle for up to 9 cycles (MPR), followed by maintenance therapy with single-agent lenalidomide (R) 10 mg PO QD on Days 1 to 21 of each 28-day cycle from cycle 10 until progressive disease (PD).
If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Induction + Maintenance MPR+p

Reporting group description:

During the double-blind induction phase, participants received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and lenalidomide (R) 10 mg PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles, followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD.
If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Induction + Maintenance MPp+p

Reporting group description:

During the double-blind induction phase, subjects received melphalan (M) 0.18 mg/kg PO QD on days 1 to 4 plus prednisone (P) 2 mg/kg PO QD on days 1 to 4 of each 28-day cycle and identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle for up to 9 cycles (MPp), followed by maintenance therapy with identically matching placebo (p) PO QD on days 1 to 21 of each 28-day cycle from cycle 10 until PD.
If participants experienced PD during the induction or maintenance treatment periods, they were given the option to be treated with lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Open-Label Extension MPR+R

Reporting group description:

For subjects who were treated with MPR+R and experienced PD during the induction or maintenance treatment periods, were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Open-Label Extension MPR+p

Reporting group description:

For subjects who were treated with MPR+p and experienced PD during the induction or maintenance treatment periods, were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21

of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Reporting group title	Open-Label Extension MPp+p

Reporting group description:

For subjects who were treated with MPp+p and experienced PD during the induction or maintenance treatment periods, were given the option to be treated with lenalidomide 25 mg PO QD on Days 1 to 21 of each 28-day cycle with or without dexamethasone 40 mg PO QD on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle at the discretion of the investigator.

Serious adverse events	Induction + Maintenance MPR+R	Induction + Maintenance MPR+p	Induction + Maintenance MPp+p
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 150 (52.67%)	66 / 152 (43.42%)	57 / 153 (37.25%)
number of deaths (all causes)	11	8	7
number of deaths resulting from adverse events	4	2	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	4 / 150 (2.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEN'S DISEASE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CANCER			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHIAL CARCINOMA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
COLON CANCER			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
KERATOACANTHOMA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
LENTIGO MALIGNA STAGE UNSPECIFIED			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKAEMIA PLASMACYTIC			
subjects affected / exposed	0 / 150 (0.00%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
LIGHT CHAIN DISEASE			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
MULTIPLE MYELOMA			
subjects affected / exposed	0 / 150 (0.00%)	3 / 152 (1.97%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 2
MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NASAL CAVITY CANCER			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
PLASMACYTOMA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
PROSTATE CANCER			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL CANCER			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
RECTAL CANCER METASTATIC			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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 CELL CARCINOMA STAGE I			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-CELL TYPE ACUTE LEUKAEMIA			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
Vascular disorders			
AORTIC DISSECTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIOVASCULAR INSUFFICIENCY			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CIRCULATORY COLLAPSE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
DEEP VEIN THROMBOSIS			
subjects affected / exposed	1 / 150 (0.67%)	6 / 152 (3.95%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	2 / 2	6 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
THROMBOSIS			

subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULITIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
VENOUS THROMBOSIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 150 (0.00%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST DISCOMFORT			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
CHEST PAIN			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
CHILLS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
DEATH			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
FACE OEDEMA			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
FATIGUE			
subjects affected / exposed	4 / 150 (2.67%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	3 / 4	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	1 / 2	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
MALAISE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MULTI-ORGAN FAILURE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			

subjects affected / exposed	8 / 150 (5.33%)	2 / 152 (1.32%)	7 / 153 (4.58%)
occurrences causally related to treatment / all	4 / 8	0 / 2	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN CARDIAC DEATH			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
BRONCHOSPASM			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
DYSPNOEA			

subjects affected / exposed	2 / 150 (1.33%)	3 / 152 (1.97%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PLEURAL EFFUSION			
subjects affected / exposed	0 / 150 (0.00%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
PULMONARY EMBOLISM			
subjects affected / exposed	2 / 150 (1.33%)	3 / 152 (1.97%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	2 / 2	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
WHEEZING			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
Psychiatric disorders			
DELIRIUM			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
DEPRESSION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
DISORIENTATION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
INSOMNIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
Investigations			
MONOCLONAL IMMUNOGLOBULIN PRESENT			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ACCIDENTAL OVERDOSE			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			

subjects affected / exposed	0 / 150 (0.00%)	2 / 152 (1.32%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
FEMUR FRACTURE			
subjects affected / exposed	0 / 150 (0.00%)	2 / 152 (1.32%)	0 / 153 (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
HEAD INJURY			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
HIP FRACTURE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
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 COMPRESSION FRACTURE			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
SPINAL FRACTURE			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
STERNAL FRACTURE			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THERAPEUTIC AGENT TOXICITY			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRAUMATIC FRACTURE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
ANGINA PECTORIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	3 / 153 (1.96%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 150 (0.67%)	3 / 152 (1.97%)	5 / 153 (3.27%)
occurrences causally related to treatment / all	1 / 1	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
BRADYCARDIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CARDIAC ARREST			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CARDIAC DISORDER			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	3 / 150 (2.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CARDIAC FAILURE CHRONIC			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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 FAILURE CONGESTIVE			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
CARDIOGENIC SHOCK			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	1 / 1
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY OCCLUSION			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PALPITATIONS			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIGHT VENTRICULAR FAILURE			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
SINUS TACHYCARDIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
TACHYARRHYTHMIA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
Nervous system disorders			
APHASIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
BRAIN OEDEMA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (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
COGNITIVE DISORDER			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
CONVULSION			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
DIABETIC COMA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
DIZZINESS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NYSTAGMUS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
PARALYSIS			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
PARKINSON'S DISEASE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST HERPETIC NEURALGIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
PRESYNCOPE			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
SCIATICA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	2 / 150 (1.33%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE VASOVAGAL			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	6 / 150 (4.00%)	8 / 152 (5.26%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	5 / 6	6 / 10	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	9 / 150 (6.00%)	2 / 152 (1.32%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	9 / 9	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
LEUKOPENIA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			
subjects affected / exposed	6 / 150 (4.00%)	4 / 152 (2.63%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	5 / 6	3 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	1 / 150 (0.67%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 150 (2.00%)	4 / 152 (2.63%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	2 / 3	2 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

VERTIGO			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINOPATHY			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
GLAUCOMA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
RETINAL DETACHMENT			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL STRANGULATED HERNIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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

COLITIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
CONSTIPATION			
subjects affected / exposed	2 / 150 (1.33%)	3 / 152 (1.97%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	3 / 150 (2.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
GASTRITIS ATROPHIC			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
GASTRITIS HAEMORRHAGIC			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
HAEMORRHOIDAL HAEMORRHAGE			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
INGUINAL HERNIA			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
MELAENA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	3 / 150 (2.00%)	2 / 152 (1.32%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	2 / 3	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATIC MASS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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	4 / 150 (2.67%)	1 / 152 (0.66%)	3 / 153 (1.96%)
occurrences causally related to treatment / all	2 / 5	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILIARY COLIC			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
CHOLESTASIS			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS TOXIC			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
ACTINIC KERATOSIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
ANGIOEDEMA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
BLISTER			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
DERMATITIS EXFOLIATIVE			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
DRUG ERUPTION			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
ERYTHEMA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
RASH			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URTICARIA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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			
DYSURIA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEPHROPATHY			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
NEPHROTIC SYNDROME			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL AMYLOIDOSIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE			

subjects affected / exposed	0 / 150 (0.00%)	3 / 152 (1.97%)	2 / 153 (1.31%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	1 / 150 (0.67%)	3 / 152 (1.97%)	4 / 153 (2.61%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
URINARY RETENTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 150 (0.67%)	2 / 152 (1.32%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHROPATHY			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE LESION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
BONE PAIN			

subjects affected / exposed	5 / 150 (3.33%)	2 / 152 (1.32%)	6 / 153 (3.92%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GOUTY ARTHRITIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
INTERVERTEBRAL DISC DISORDER			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
MUSCLE HAEMORRHAGE			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOSITIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
OSTEOARTHRITIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
PATHOLOGICAL FRACTURE			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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			
APPENDICITIS			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS INFECTIVE			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
BRONCHITIS			
subjects affected / exposed	1 / 150 (0.67%)	2 / 152 (1.32%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS BACTERIAL			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
BRONCHOPNEUMONIA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
CAMPYLOBACTER INFECTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARBUNCLE			

subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
CELLULITIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM COLITIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
CRYPTOCOCCOSIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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 / 150 (0.67%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
ESCHERICHIA INFECTION			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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 SEPSIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
GASTROENTERITIS NORWALK VIRUS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
HERPES SIMPLEX			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
HERPES ZOSTER			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (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
INFECTION			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
LOBAR PNEUMONIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
LOWER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
MENINGITIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	6 / 150 (4.00%)	8 / 152 (5.26%)	8 / 153 (5.23%)
occurrences causally related to treatment / all	5 / 7	6 / 9	3 / 9
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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 STAPHYLOCOCCAL			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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
POST PROCEDURAL INFECTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSEUDOMEMBRANOUS COLITIS			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PYELONEPHRITIS CHRONIC			

subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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	1 / 150 (0.67%)	3 / 152 (1.97%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPTIC SHOCK			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
SINUSITIS			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STREPTOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
STREPTOCOCCAL SEPSIS			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			

subjects affected / exposed	2 / 150 (1.33%)	0 / 152 (0.00%)	3 / 153 (1.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
WOUND INFECTION			
subjects affected / exposed	0 / 150 (0.00%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
ANOREXIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
DEHYDRATION			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS			
subjects affected / exposed	1 / 150 (0.67%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (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	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERKALAEMIA			
subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOCALCAEMIA			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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
HYPOKALAEMIA			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL INTAKE REDUCED			
subjects affected / exposed	1 / 150 (0.67%)	0 / 152 (0.00%)	0 / 153 (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

Serious adverse events	Open-Label Extension MPR+R	Open-Label Extension MPR+p	Open-Label Extension MPp+p
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 23 (47.83%)	21 / 53 (39.62%)	39 / 80 (48.75%)
number of deaths (all causes)	2	10	7
number of deaths resulting from adverse events	0	0	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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

BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	3 / 80 (3.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEN'S DISEASE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BREAST CANCER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BRONCHIAL CARCINOMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
COLON CANCER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
KERATOACANTHOMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LENTIGO MALIGNA STAGE UNSPECIFIED			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
LEUKAEMIA PLASMACYTIC			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
LIGHT CHAIN DISEASE			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
LUNG NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
MULTIPLE MYELOMA			
subjects affected / exposed	1 / 23 (4.35%)	2 / 53 (3.77%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
NASAL CAVITY CANCER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PLASMACYTOMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PROSTATE CANCER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
RECTAL CANCER			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
RECTAL CANCER METASTATIC			

subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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 CELL CARCINOMA STAGE I			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	3 / 80 (3.75%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
T-CELL TYPE ACUTE LEUKAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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			
AORTIC DISSECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CARDIOVASCULAR INSUFFICIENCY			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CIRCULATORY COLLAPSE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
DEEP VEIN THROMBOSIS			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HYPOTENSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
THROMBOSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
VASCULITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
VENOUS THROMBOSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
CHEST DISCOMFORT			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CHILLS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DEATH			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
FACE OEDEMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
FATIGUE			
subjects affected / exposed	2 / 23 (8.70%)	2 / 53 (3.77%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALAISE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
MULTI-ORGAN FAILURE			

subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PAIN			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PYREXIA			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN CARDIAC DEATH			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
Reproductive system and breast disorders			

BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BRONCHOSPASM			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DYSPNOEA			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 ASPIRATION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
WHEEZING			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DEPRESSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DISORIENTATION			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
INSOMNIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PSYCHOTIC DISORDER DUE TO A GENERAL MEDICAL CONDITION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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			
MONOCLONAL IMMUNOGLOBULIN PRESENT			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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			
ACCIDENTAL OVERDOSE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
FALL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	0 / 80 (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
FEMUR FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEAD INJURY			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HIP FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HUMERUS FRACTURE			

subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STERNAL FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
TENDON RUPTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
THERAPEUTIC AGENT TOXICITY			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
TRAUMATIC FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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			
ACUTE CORONARY SYNDROME			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ANGINA PECTORIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ANGINA UNSTABLE			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ATRIOVENTRICULAR BLOCK			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
BRADYCARDIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 DISORDER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 FAILURE			
subjects affected / exposed	1 / 23 (4.35%)	2 / 53 (3.77%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
CARDIAC FAILURE CHRONIC			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CARDIOGENIC SHOCK			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CORONARY ARTERY DISEASE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CORONARY ARTERY OCCLUSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
MYOCARDIAL INFARCTION			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PALPITATIONS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
SINUS TACHYCARDIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
TACHYARRHYTHMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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			
APHASIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BRAIN OEDEMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
CEREBRAL HAEMORRHAGE			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CEREBRAL ISCHAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COGNITIVE DISORDER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CONVULSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DIABETIC COMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DIZZINESS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HEMIPARESIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC STROKE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METABOLIC ENCEPHALOPATHY			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
NEUROPATHY PERIPHERAL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
NYSTAGMUS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PARALYSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARKINSON'S DISEASE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
POST HERPETIC NEURALGIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PRESYNCOPE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
SCIATICA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
SUBARACHNOID HAEMORRHAGE			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
SYNCOPE VASOVAGAL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
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			
ANAEMIA			
subjects affected / exposed	2 / 23 (8.70%)	3 / 53 (5.66%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	3 / 3	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
LEUKOPENIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
NEUTROPENIA			

subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCYTOPENIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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	1 / 23 (4.35%)	1 / 53 (1.89%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
DIABETIC RETINOPATHY			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GLAUCOMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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			

ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ABDOMINAL STRANGULATED HERNIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
COLITIS			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
CONSTIPATION			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
DIARRHOEA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
GASTRITIS ATROPHIC			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
GASTRITIS HAEMORRHAGIC			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 HAEMORRHAGE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 OBSTRUCTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HAEMORRHOIDAL HAEMORRHAGE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ILEUS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
INGUINAL HERNIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
MELAENA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PANCREATIC MASS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
RECTAL HAEMORRHAGE			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
VOMITING			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
Hepatobiliary disorders			
BILIARY COLIC			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CHOLESTASIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HEPATITIS TOXIC			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
Skin and subcutaneous tissue disorders			
ACTINIC KERATOSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGIOEDEMA			

subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
BLISTER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DERMATITIS EXFOLIATIVE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DRUG ERUPTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ERYTHEMA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
RASH			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
URTICARIA			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (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
Renal and urinary disorders			
DYSURIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
NEPHROPATHY			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
NEPHROTIC SYNDROME			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 AMYLOIDOSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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	0 / 23 (0.00%)	1 / 53 (1.89%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 RETENTION			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ARTHRITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ARTHROPATHY			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BACK PAIN			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE LESION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 PAIN			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GOUTY ARTHRITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
INTERVERTEBRAL DISC DISORDER			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
MUSCLE HAEMORRHAGE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOSITIS			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
OSTEOARTHRITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
APPENDICITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ARTHRITIS INFECTIVE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BRONCHITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BRONCHITIS BACTERIAL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
BRONCHOPNEUMONIA			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CAMPYLOBACTER INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CARBUNCLE			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CELLULITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM COLITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CRYPTOCOCCOSIS			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
CYSTITIS			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DIVERTICULITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ERYSIPELAS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS NORWALK VIRUS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HERPES SIMPLEX			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HERPES ZOSTER			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
LOBAR PNEUMONIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
MENINGITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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	0 / 23 (0.00%)	3 / 53 (5.66%)	6 / 80 (7.50%)
occurrences causally related to treatment / all	0 / 0	0 / 3	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 2	1 / 1
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA STAPHYLOCOCCAL			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
POST PROCEDURAL INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PSEUDOMEMBRANOUS COLITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
PYELONEPHRITIS CHRONIC			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SEPSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
SEPTIC SHOCK			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SINUSITIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
STREPTOCOCCAL BACTERAEMIA			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
STREPTOCOCCAL SEPSIS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
WOUND INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
Metabolism and nutrition disorders			
ANOREXIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DEHYDRATION			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (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
DIABETES MELLITUS			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERKALAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HYPOCALCAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
HYPOKALAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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
ORAL INTAKE REDUCED			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	0 / 80 (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: 5 %

Non-serious adverse events	Induction + Maintenance MPR+R	Induction + Maintenance MPR+p	Induction + Maintenance MPp+p
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 150 (100.00%)	150 / 152 (98.68%)	150 / 153 (98.04%)
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	4 / 150 (2.67%)	9 / 152 (5.92%)	1 / 153 (0.65%)
occurrences (all)	4	12	1
HYPERTENSION			
subjects affected / exposed	8 / 150 (5.33%)	9 / 152 (5.92%)	13 / 153 (8.50%)
occurrences (all)	9	10	24
HYPOTENSION			
subjects affected / exposed	10 / 150 (6.67%)	4 / 152 (2.63%)	10 / 153 (6.54%)
occurrences (all)	13	4	10
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	34 / 150 (22.67%)	22 / 152 (14.47%)	24 / 153 (15.69%)
occurrences (all)	80	37	38
FATIGUE			
subjects affected / exposed	52 / 150 (34.67%)	53 / 152 (34.87%)	59 / 153 (38.56%)
occurrences (all)	151	105	107
MALAISE			
subjects affected / exposed	2 / 150 (1.33%)	1 / 152 (0.66%)	4 / 153 (2.61%)
occurrences (all)	4	4	4
OEDEMA			
subjects affected / exposed	6 / 150 (4.00%)	11 / 152 (7.24%)	5 / 153 (3.27%)
occurrences (all)	11	13	9
OEDEMA PERIPHERAL			
subjects affected / exposed	31 / 150 (20.67%)	38 / 152 (25.00%)	29 / 153 (18.95%)
occurrences (all)	52	63	49

PYREXIA			
subjects affected / exposed	34 / 150 (22.67%)	40 / 152 (26.32%)	32 / 153 (20.92%)
occurrences (all)	54	65	39
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	36 / 150 (24.00%)	29 / 152 (19.08%)	22 / 153 (14.38%)
occurrences (all)	52	35	30
DYSPHONIA			
subjects affected / exposed	4 / 150 (2.67%)	4 / 152 (2.63%)	5 / 153 (3.27%)
occurrences (all)	4	4	6
DYSPNOEA			
subjects affected / exposed	22 / 150 (14.67%)	14 / 152 (9.21%)	19 / 153 (12.42%)
occurrences (all)	36	19	23
DYSPNOEA EXERTIONAL			
subjects affected / exposed	4 / 150 (2.67%)	3 / 152 (1.97%)	3 / 153 (1.96%)
occurrences (all)	6	4	6
EPISTAXIS			
subjects affected / exposed	9 / 150 (6.00%)	7 / 152 (4.61%)	11 / 153 (7.19%)
occurrences (all)	25	10	16
PHARYNGOLARYNGEAL PAIN			
subjects affected / exposed	6 / 150 (4.00%)	10 / 152 (6.58%)	9 / 153 (5.88%)
occurrences (all)	9	11	11
Psychiatric disorders			
AGITATION			
subjects affected / exposed	3 / 150 (2.00%)	4 / 152 (2.63%)	0 / 153 (0.00%)
occurrences (all)	3	5	0
ANXIETY			
subjects affected / exposed	3 / 150 (2.00%)	5 / 152 (3.29%)	1 / 153 (0.65%)
occurrences (all)	3	6	1
DEPRESSION			
subjects affected / exposed	9 / 150 (6.00%)	18 / 152 (11.84%)	10 / 153 (6.54%)
occurrences (all)	13	19	10
INSOMNIA			
subjects affected / exposed	17 / 150 (11.33%)	22 / 152 (14.47%)	22 / 153 (14.38%)
occurrences (all)	18	25	35
Investigations			

BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	7 / 150 (4.67%)	11 / 152 (7.24%)	5 / 153 (3.27%)
occurrences (all)	13	23	8
BLOOD CREATININE INCREASED			
subjects affected / exposed	16 / 150 (10.67%)	6 / 152 (3.95%)	17 / 153 (11.11%)
occurrences (all)	35	7	37
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	4 / 150 (2.67%)	8 / 152 (5.26%)	2 / 153 (1.31%)
occurrences (all)	7	13	2
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 150 (0.67%)	5 / 152 (3.29%)	0 / 153 (0.00%)
occurrences (all)	5	11	0
WEIGHT DECREASED			
subjects affected / exposed	9 / 150 (6.00%)	14 / 152 (9.21%)	9 / 153 (5.88%)
occurrences (all)	11	19	11
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	4 / 150 (2.67%)	6 / 152 (3.95%)	11 / 153 (7.19%)
occurrences (all)	6	9	12
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	0 / 150 (0.00%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences (all)	0	2	1
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	16 / 150 (10.67%)	21 / 152 (13.82%)	16 / 153 (10.46%)
occurrences (all)	24	22	21
DYSGEUSIA			
subjects affected / exposed	6 / 150 (4.00%)	10 / 152 (6.58%)	7 / 153 (4.58%)
occurrences (all)	9	13	7
HEADACHE			
subjects affected / exposed	12 / 150 (8.00%)	16 / 152 (10.53%)	22 / 153 (14.38%)
occurrences (all)	35	29	22
PARAESTHESIA			

subjects affected / exposed	15 / 150 (10.00%)	10 / 152 (6.58%)	6 / 153 (3.92%)
occurrences (all)	20	18	8
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	12 / 150 (8.00%)	10 / 152 (6.58%)	5 / 153 (3.27%)
occurrences (all)	18	13	11
SCIATICA			
subjects affected / exposed	5 / 150 (3.33%)	2 / 152 (1.32%)	4 / 153 (2.61%)
occurrences (all)	5	2	6
TREMOR			
subjects affected / exposed	9 / 150 (6.00%)	4 / 152 (2.63%)	6 / 153 (3.92%)
occurrences (all)	11	4	6
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	106 / 150 (70.67%)	96 / 152 (63.16%)	83 / 153 (54.25%)
occurrences (all)	506	374	313
LEUKOPENIA			
subjects affected / exposed	54 / 150 (36.00%)	59 / 152 (38.82%)	50 / 153 (32.68%)
occurrences (all)	499	461	249
LYMPHOPENIA			
subjects affected / exposed	2 / 150 (1.33%)	4 / 152 (2.63%)	4 / 153 (2.61%)
occurrences (all)	42	6	33
NEUTROPENIA			
subjects affected / exposed	124 / 150 (82.67%)	118 / 152 (77.63%)	79 / 153 (51.63%)
occurrences (all)	1093	837	409
THROMBOCYTOPENIA			
subjects affected / exposed	105 / 150 (70.00%)	104 / 152 (68.42%)	69 / 153 (45.10%)
occurrences (all)	598	558	285
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	15 / 150 (10.00%)	10 / 152 (6.58%)	14 / 153 (9.15%)
occurrences (all)	26	13	25
Eye disorders			
CATARACT			
subjects affected / exposed	3 / 150 (2.00%)	1 / 152 (0.66%)	2 / 153 (1.31%)
occurrences (all)	4	1	2
Gastrointestinal disorders			

ABDOMINAL PAIN			
subjects affected / exposed	18 / 150 (12.00%)	9 / 152 (5.92%)	7 / 153 (4.58%)
occurrences (all)	31	9	8
ABDOMINAL PAIN UPPER			
subjects affected / exposed	15 / 150 (10.00%)	7 / 152 (4.61%)	13 / 153 (8.50%)
occurrences (all)	24	9	21
CONSTIPATION			
subjects affected / exposed	50 / 150 (33.33%)	39 / 152 (25.66%)	38 / 153 (24.84%)
occurrences (all)	86	70	58
DIARRHOEA			
subjects affected / exposed	50 / 150 (33.33%)	37 / 152 (24.34%)	39 / 153 (25.49%)
occurrences (all)	164	65	52
DRY MOUTH			
subjects affected / exposed	13 / 150 (8.67%)	8 / 152 (5.26%)	5 / 153 (3.27%)
occurrences (all)	15	9	7
DYSPEPSIA			
subjects affected / exposed	14 / 150 (9.33%)	7 / 152 (4.61%)	8 / 153 (5.23%)
occurrences (all)	20	7	10
NAUSEA			
subjects affected / exposed	40 / 150 (26.67%)	40 / 152 (26.32%)	54 / 153 (35.29%)
occurrences (all)	73	69	99
VOMITING			
subjects affected / exposed	18 / 150 (12.00%)	19 / 152 (12.50%)	21 / 153 (13.73%)
occurrences (all)	28	28	34
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	4 / 150 (2.67%)	3 / 152 (1.97%)	8 / 153 (5.23%)
occurrences (all)	4	4	9
DRY SKIN			
subjects affected / exposed	8 / 150 (5.33%)	3 / 152 (1.97%)	10 / 153 (6.54%)
occurrences (all)	9	3	12
HYPERHIDROSIS			
subjects affected / exposed	9 / 150 (6.00%)	6 / 152 (3.95%)	8 / 153 (5.23%)
occurrences (all)	12	7	9
NIGHT SWEATS			

subjects affected / exposed	5 / 150 (3.33%)	9 / 152 (5.92%)	6 / 153 (3.92%)
occurrences (all)	9	11	11
PRURITUS			
subjects affected / exposed	16 / 150 (10.67%)	12 / 152 (7.89%)	10 / 153 (6.54%)
occurrences (all)	25	15	11
RASH			
subjects affected / exposed	31 / 150 (20.67%)	43 / 152 (28.29%)	13 / 153 (8.50%)
occurrences (all)	61	64	14
Renal and urinary disorders			
PROTEINURIA			
subjects affected / exposed	4 / 150 (2.67%)	8 / 152 (5.26%)	7 / 153 (4.58%)
occurrences (all)	14	17	14
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	17 / 150 (11.33%)	21 / 152 (13.82%)	17 / 153 (11.11%)
occurrences (all)	20	31	24
BACK PAIN			
subjects affected / exposed	24 / 150 (16.00%)	20 / 152 (13.16%)	35 / 153 (22.88%)
occurrences (all)	31	28	45
BONE PAIN			
subjects affected / exposed	50 / 150 (33.33%)	47 / 152 (30.92%)	51 / 153 (33.33%)
occurrences (all)	118	82	87
MUSCLE SPASMS			
subjects affected / exposed	19 / 150 (12.67%)	18 / 152 (11.84%)	10 / 153 (6.54%)
occurrences (all)	35	39	10
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	12 / 150 (8.00%)	9 / 152 (5.92%)	5 / 153 (3.27%)
occurrences (all)	13	12	6
MUSCULOSKELETAL PAIN			
subjects affected / exposed	25 / 150 (16.67%)	18 / 152 (11.84%)	21 / 153 (13.73%)
occurrences (all)	47	25	40
MYALGIA			
subjects affected / exposed	5 / 150 (3.33%)	10 / 152 (6.58%)	3 / 153 (1.96%)
occurrences (all)	6	16	3
NECK PAIN			

subjects affected / exposed	7 / 150 (4.67%)	2 / 152 (1.32%)	7 / 153 (4.58%)
occurrences (all)	8	2	10
OSTEOARTHRITIS			
subjects affected / exposed	1 / 150 (0.67%)	3 / 152 (1.97%)	6 / 153 (3.92%)
occurrences (all)	1	4	6
PAIN IN EXTREMITY			
subjects affected / exposed	14 / 150 (9.33%)	9 / 152 (5.92%)	13 / 153 (8.50%)
occurrences (all)	20	15	18
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	19 / 150 (12.67%)	17 / 152 (11.18%)	12 / 153 (7.84%)
occurrences (all)	35	22	16
CYSTITIS			
subjects affected / exposed	6 / 150 (4.00%)	7 / 152 (4.61%)	8 / 153 (5.23%)
occurrences (all)	13	8	15
HERPES ZOSTER			
subjects affected / exposed	0 / 150 (0.00%)	3 / 152 (1.97%)	8 / 153 (5.23%)
occurrences (all)	0	3	8
INFLUENZA			
subjects affected / exposed	6 / 150 (4.00%)	5 / 152 (3.29%)	3 / 153 (1.96%)
occurrences (all)	6	5	3
NASOPHARYNGITIS			
subjects affected / exposed	30 / 150 (20.00%)	22 / 152 (14.47%)	26 / 153 (16.99%)
occurrences (all)	49	38	36
ORAL HERPES			
subjects affected / exposed	8 / 150 (5.33%)	6 / 152 (3.95%)	6 / 153 (3.92%)
occurrences (all)	8	7	6
PNEUMONIA			
subjects affected / exposed	4 / 150 (2.67%)	6 / 152 (3.95%)	7 / 153 (4.58%)
occurrences (all)	4	6	7
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	10 / 150 (6.67%)	6 / 152 (3.95%)	3 / 153 (1.96%)
occurrences (all)	12	8	3
RESPIRATORY TRACT INFECTION VIRAL			

subjects affected / exposed	0 / 150 (0.00%)	0 / 152 (0.00%)	0 / 153 (0.00%)
occurrences (all)	0	0	0
RHINITIS			
subjects affected / exposed	9 / 150 (6.00%)	5 / 152 (3.29%)	6 / 153 (3.92%)
occurrences (all)	13	10	6
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	20 / 150 (13.33%)	20 / 152 (13.16%)	15 / 153 (9.80%)
occurrences (all)	30	27	21
URINARY TRACT INFECTION			
subjects affected / exposed	17 / 150 (11.33%)	13 / 152 (8.55%)	12 / 153 (7.84%)
occurrences (all)	24	18	14
VIRAL INFECTION			
subjects affected / exposed	7 / 150 (4.67%)	2 / 152 (1.32%)	1 / 153 (0.65%)
occurrences (all)	7	2	1
Metabolism and nutrition disorders			
ANOREXIA			
subjects affected / exposed	24 / 150 (16.00%)	36 / 152 (23.68%)	23 / 153 (15.03%)
occurrences (all)	40	54	28
HYPERGLYCAEMIA			
subjects affected / exposed	11 / 150 (7.33%)	11 / 152 (7.24%)	18 / 153 (11.76%)
occurrences (all)	45	42	51
HYPERURICAEMIA			
subjects affected / exposed	10 / 150 (6.67%)	5 / 152 (3.29%)	6 / 153 (3.92%)
occurrences (all)	14	9	9
HYPOCALCAEMIA			
subjects affected / exposed	14 / 150 (9.33%)	9 / 152 (5.92%)	10 / 153 (6.54%)
occurrences (all)	18	20	26
HYPOKALAEMIA			
subjects affected / exposed	19 / 150 (12.67%)	11 / 152 (7.24%)	6 / 153 (3.92%)
occurrences (all)	24	20	6

Non-serious adverse events	Open-Label Extension MPR+R	Open-Label Extension MPR+p	Open-Label Extension MPp+p
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 23 (91.30%)	48 / 53 (90.57%)	76 / 80 (95.00%)
Vascular disorders			

DEEP VEIN THROMBOSIS			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	4 / 80 (5.00%)
occurrences (all)	2	2	4
HYPERTENSION			
subjects affected / exposed	3 / 23 (13.04%)	2 / 53 (3.77%)	2 / 80 (2.50%)
occurrences (all)	5	6	2
HYPOTENSION			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	3 / 80 (3.75%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	4 / 23 (17.39%)	6 / 53 (11.32%)	9 / 80 (11.25%)
occurrences (all)	5	18	32
FATIGUE			
subjects affected / exposed	6 / 23 (26.09%)	15 / 53 (28.30%)	23 / 80 (28.75%)
occurrences (all)	8	29	53
MALAISE			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	2 / 80 (2.50%)
occurrences (all)	0	6	2
OEDEMA			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	2 / 80 (2.50%)
occurrences (all)	0	1	5
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 23 (4.35%)	9 / 53 (16.98%)	21 / 80 (26.25%)
occurrences (all)	1	15	33
PYREXIA			
subjects affected / exposed	3 / 23 (13.04%)	7 / 53 (13.21%)	10 / 80 (12.50%)
occurrences (all)	6	12	14
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	1 / 23 (4.35%)	5 / 53 (9.43%)	12 / 80 (15.00%)
occurrences (all)	1	5	16
DYSPHONIA			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	5 / 80 (6.25%)
occurrences (all)	0	1	5
DYSPNOEA			

subjects affected / exposed	1 / 23 (4.35%)	8 / 53 (15.09%)	10 / 80 (12.50%)
occurrences (all)	2	11	16
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 23 (0.00%)	5 / 53 (9.43%)	2 / 80 (2.50%)
occurrences (all)	0	7	3
EPISTAXIS			
subjects affected / exposed	3 / 23 (13.04%)	3 / 53 (5.66%)	2 / 80 (2.50%)
occurrences (all)	3	4	3
PHARYNGOLARYNGEAL PAIN			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	4 / 80 (5.00%)
occurrences (all)	0	5	6
Psychiatric disorders			
AGITATION			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	3 / 80 (3.75%)
occurrences (all)	0	3	4
ANXIETY			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	2 / 80 (2.50%)
occurrences (all)	0	3	2
DEPRESSION			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	4 / 80 (5.00%)
occurrences (all)	1	6	4
INSOMNIA			
subjects affected / exposed	5 / 23 (21.74%)	3 / 53 (5.66%)	11 / 80 (13.75%)
occurrences (all)	6	6	12
Investigations			
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	0 / 80 (0.00%)
occurrences (all)	1	9	0
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	4 / 80 (5.00%)
occurrences (all)	0	1	6
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	3 / 80 (3.75%)
occurrences (all)	1	1	9
GAMMA-GLUTAMYLTRANSFERASE INCREASED			

subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	0 / 80 (0.00%)
occurrences (all)	0	8	0
WEIGHT DECREASED			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	6 / 80 (7.50%)
occurrences (all)	0	0	7
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	2 / 80 (2.50%)
occurrences (all)	0	6	2
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	2 / 80 (2.50%)
occurrences (all)	0	5	2
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 23 (4.35%)	4 / 53 (7.55%)	10 / 80 (12.50%)
occurrences (all)	1	6	13
DYSGEUSIA			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	3 / 80 (3.75%)
occurrences (all)	0	3	11
HEADACHE			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	4 / 80 (5.00%)
occurrences (all)	0	5	5
PARAESTHESIA			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	1 / 80 (1.25%)
occurrences (all)	6	3	1
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	0 / 23 (0.00%)	6 / 53 (11.32%)	2 / 80 (2.50%)
occurrences (all)	0	7	6
SCIATICA			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	4 / 80 (5.00%)
occurrences (all)	0	1	6
TREMOR			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	6 / 80 (7.50%)
occurrences (all)	1	0	7
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	11 / 23 (47.83%)	21 / 53 (39.62%)	41 / 80 (51.25%)
occurrences (all)	24	57	126
LEUKOPENIA			
subjects affected / exposed	7 / 23 (30.43%)	22 / 53 (41.51%)	27 / 80 (33.75%)
occurrences (all)	23	80	129
LYMPHOPENIA			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	5 / 80 (6.25%)
occurrences (all)	6	1	19
NEUTROPENIA			
subjects affected / exposed	14 / 23 (60.87%)	38 / 53 (71.70%)	57 / 80 (71.25%)
occurrences (all)	36	185	268
THROMBOCYTOPENIA			
subjects affected / exposed	13 / 23 (56.52%)	25 / 53 (47.17%)	33 / 80 (41.25%)
occurrences (all)	26	60	96
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	8 / 80 (10.00%)
occurrences (all)	0	4	9
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	3 / 80 (3.75%)
occurrences (all)	0	4	3
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	1 / 23 (4.35%)	2 / 53 (3.77%)	3 / 80 (3.75%)
occurrences (all)	1	3	7
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	2 / 80 (2.50%)
occurrences (all)	1	4	2
CONSTIPATION			
subjects affected / exposed	3 / 23 (13.04%)	9 / 53 (16.98%)	21 / 80 (26.25%)
occurrences (all)	4	15	40
DIARRHOEA			
subjects affected / exposed	5 / 23 (21.74%)	9 / 53 (16.98%)	19 / 80 (23.75%)
occurrences (all)	9	33	28
DRY MOUTH			

subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	2 / 80 (2.50%)
occurrences (all)	0	2	3
DYSPEPSIA			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	1 / 80 (1.25%)
occurrences (all)	1	1	1
NAUSEA			
subjects affected / exposed	4 / 23 (17.39%)	4 / 53 (7.55%)	8 / 80 (10.00%)
occurrences (all)	5	7	9
VOMITING			
subjects affected / exposed	1 / 23 (4.35%)	2 / 53 (3.77%)	4 / 80 (5.00%)
occurrences (all)	2	2	5
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	1 / 23 (4.35%)	0 / 53 (0.00%)	0 / 80 (0.00%)
occurrences (all)	1	0	0
DRY SKIN			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	4 / 80 (5.00%)
occurrences (all)	0	1	4
HYPERHIDROSIS			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	1 / 80 (1.25%)
occurrences (all)	0	6	1
NIGHT SWEATS			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	3 / 80 (3.75%)
occurrences (all)	0	0	3
PRURITUS			
subjects affected / exposed	0 / 23 (0.00%)	5 / 53 (9.43%)	5 / 80 (6.25%)
occurrences (all)	0	8	5
RASH			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	16 / 80 (20.00%)
occurrences (all)	0	2	27
Renal and urinary disorders			
PROTEINURIA			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	3 / 80 (3.75%)
occurrences (all)	3	5	4
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	0 / 23 (0.00%)	4 / 53 (7.55%)	7 / 80 (8.75%)
occurrences (all)	0	5	9
BACK PAIN			
subjects affected / exposed	1 / 23 (4.35%)	5 / 53 (9.43%)	13 / 80 (16.25%)
occurrences (all)	1	9	16
BONE PAIN			
subjects affected / exposed	5 / 23 (21.74%)	13 / 53 (24.53%)	20 / 80 (25.00%)
occurrences (all)	6	18	33
MUSCLE SPASMS			
subjects affected / exposed	0 / 23 (0.00%)	6 / 53 (11.32%)	15 / 80 (18.75%)
occurrences (all)	0	10	20
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	2 / 80 (2.50%)
occurrences (all)	0	2	2
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 23 (4.35%)	8 / 53 (15.09%)	7 / 80 (8.75%)
occurrences (all)	1	14	10
MYALGIA			
subjects affected / exposed	3 / 23 (13.04%)	1 / 53 (1.89%)	3 / 80 (3.75%)
occurrences (all)	3	1	5
NECK PAIN			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	1 / 80 (1.25%)
occurrences (all)	0	5	1
OSTEOARTHRITIS			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	0 / 80 (0.00%)
occurrences (all)	0	3	0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	4 / 80 (5.00%)
occurrences (all)	0	2	4
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 23 (8.70%)	6 / 53 (11.32%)	6 / 80 (7.50%)
occurrences (all)	3	6	7
CYSTITIS			

subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	1 / 80 (1.25%)
occurrences (all)	0	0	1
HERPES ZOSTER			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	2 / 80 (2.50%)
occurrences (all)	0	1	2
INFLUENZA			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	6 / 80 (7.50%)
occurrences (all)	0	3	7
NASOPHARYNGITIS			
subjects affected / exposed	2 / 23 (8.70%)	6 / 53 (11.32%)	10 / 80 (12.50%)
occurrences (all)	4	11	17
ORAL HERPES			
subjects affected / exposed	0 / 23 (0.00%)	0 / 53 (0.00%)	3 / 80 (3.75%)
occurrences (all)	0	0	17
PNEUMONIA			
subjects affected / exposed	1 / 23 (4.35%)	2 / 53 (3.77%)	6 / 80 (7.50%)
occurrences (all)	1	2	6
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 23 (8.70%)	1 / 53 (1.89%)	4 / 80 (5.00%)
occurrences (all)	2	5	5
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 23 (4.35%)	3 / 53 (5.66%)	0 / 80 (0.00%)
occurrences (all)	1	3	0
RHINITIS			
subjects affected / exposed	1 / 23 (4.35%)	2 / 53 (3.77%)	0 / 80 (0.00%)
occurrences (all)	1	3	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	7 / 80 (8.75%)
occurrences (all)	0	15	30
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 23 (4.35%)	5 / 53 (9.43%)	3 / 80 (3.75%)
occurrences (all)	1	6	7
VIRAL INFECTION			

subjects affected / exposed	0 / 23 (0.00%)	3 / 53 (5.66%)	0 / 80 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
ANOREXIA			
subjects affected / exposed	0 / 23 (0.00%)	8 / 53 (15.09%)	8 / 80 (10.00%)
occurrences (all)	0	11	9
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	1 / 53 (1.89%)	7 / 80 (8.75%)
occurrences (all)	0	1	15
HYPERURICAEMIA			
subjects affected / exposed	1 / 23 (4.35%)	1 / 53 (1.89%)	0 / 80 (0.00%)
occurrences (all)	1	1	0
HYPOCALCAEMIA			
subjects affected / exposed	2 / 23 (8.70%)	0 / 53 (0.00%)	6 / 80 (7.50%)
occurrences (all)	2	0	10
HYPOKALAEMIA			
subjects affected / exposed	0 / 23 (0.00%)	2 / 53 (3.77%)	4 / 80 (5.00%)
occurrences (all)	0	2	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2008	1. Clarified Myeloma Response Determination Criteria for progressive disease for subjects who did not achieve CR 2. Clarified procedural changes to best reflect clinical practice 3. Added language for the Lenalidomide Pregnancy Prevention Risk Management Plan 4. Added contact information for Central Laboratory for Cytogenetics 5. Updated address of Celgene emergency contact and Celgene personnel 6. Corrected prior administrative errors
27 January 2009	1. Clarified the conditions around interim analysis at 50% information 2. Added another interim analysis at 70% information
04 January 2010	1. Described changes in the study design and the procedures to be followed after unblinding for subjects in the different treatment arms; 2. described the change of treatment for subjects in the different treatment arms after unblinding (Subjects in Arm MPR+R could continue lenalidomide maintenance as open label therapy, those in Arms MPR+p and MPp+p were to stop treatment with placebo); 3. Clarified procedures to follow for emergency unblinding during the induction + maintenance phase;described the study drug given during the induct+maintenance periods; 4. Clarified supplies of melphalan and prednisone will be commercial and how they will be labeled; 5. Clarified the dosing regimens to follow after unblinding; clarified dose reduction steps for lenalidomide during the induction and maintenance periods after unblinding; 6. Clarified dose modification guidelines for hematologic toxicity during the induction and maintenance periods after unblinding; 7. Clarified the antithrombotic therapy to be used during the induct+maint periods after unblinding; 8. Clarified on when efficacy, safety, and other assessments should be performed; 9. Described the assessments to be performed during the observation phase (subjects in Arms MPR+p and MPp+p entered into the observation phase following unblinding);10. Provided for more frequent follow-up OS and subsequent antimyeloma treatment regimens for subjects in the follow-up phase; 11. Clarified storage of the study drug; clarified the requirement for a repeat bone marrow aspiration to confirm a CR per EBMT criteria; 12. Clarified the collection of M-protein data; 13. Clarified definition of the efficacy-evaluable population; 14. Provided further clarification for analysis of the PFS; 15. Clarified that "50% information" and "70% information" can only be approximate, since the actual number of events may change slightly as a result of adjudication review and further data cleaning; 16. Updated study contact information
10 February 2011	1. Modified the requirements of the follow-up phase to ensure that subjects who discontinued study therapy for any reason other than disease progression (even if they went on to receive next-line therapy) continued to be followed until disease progression, including the survival follow-up phase 2. Required that Secondary primary malignancies (SPMs) be treated as serious adverse events (SAEs) and reported throughout the study duration, including the survival follow-up phase 3. Added a central review of all hematologic SPMs 4. Updated study contact information
11 October 2011	1. In addition to the SPM reporting requirements and hematologic SPM central review requirements outlined in Amendment 4, for subjects with any SPM (solid tumors and hematologic malignancies), Amendment 5 also mandated submission of diagnostic reports (eg, pathology reports) from tumor biopsy samples collected at the SPM diagnosis to Celgene or a designee for secondary confirmation. 2. Added the collection of samples for exploratory biomarker studies, in agreement with health authorities (EMA and FDA), to assess subjects for possible molecular risk factors and to examine whether there is any correlation of molecular and genetic risk factors with the potential development of SPMs during and after lenalidomide treatment 3. Updated study contact information 4. Recorded staffing changes and added new central laboratory contacts for sample storage and exploratory laboratory studies

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23242595

http://www.ncbi.nlm.nih.gov/pubmed/22571200