

**Clinical trial results:**

**A Phase III, Randomized, Open-Label, 3-Arm Study To Determine the Efficacy and Safety of Lenalidomide (Revlimid®) Plus Low-Dose Dexamethasone When Given Until Progressive Disease or for 18 Four-Week Cycles Versus the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-Week Cycles in Patients with Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation (IFM 07-01)**

**Summary**

EudraCT number	2007-004823-39
Trial protocol	FR GB IE IT AT ES SE BE PT DE GR
Global end of trial date	14 July 2016

**Results information**

Result version number	v1 (current)
This version publication date	12 August 2017
First version publication date	12 August 2017

**Trial information****Trial identification**

Sponsor protocol code	CC-5013-MM-020
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, 01 888-260-1599, ClinicalTrialDisclosure@celgene.com
Scientific contact	Annette Ervin-Haynes, Executive Director, Clinical Research and Development, 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	14 July 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 July 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare the efficacy of lenalidomide plus low-dose dexamethasone given until progressive disease to that of the combination of melphalan, prednisone, and thalidomide given for 12 six week cycles.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 August 2008
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	Korea, Republic of: 56
Country: Number of subjects enrolled	China: 47
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	France: 459
Country: Number of subjects enrolled	Italy: 148
Country: Number of subjects enrolled	Germany: 97
Country: Number of subjects enrolled	Spain: 87
Country: Number of subjects enrolled	Greece: 86
Country: Number of subjects enrolled	United Kingdom: 71
Country: Number of subjects enrolled	Belgium: 52
Country: Number of subjects enrolled	Austria: 41
Country: Number of subjects enrolled	Portugal: 27
Country: Number of subjects enrolled	Switzerland: 26
Country: Number of subjects enrolled	Sweden: 19
Country: Number of subjects enrolled	Canada: 252
Country: Number of subjects enrolled	Australia: 72
Country: Number of subjects enrolled	United States: 60

Country: Number of subjects enrolled	New Zealand: 12
Worldwide total number of subjects	1623
EEA total number of subjects	1087

Notes:

<b>Subjects enrolled per age group</b>	
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)	92
From 65 to 84 years	1475
85 years and over	56

## Subject disposition

### Recruitment

#### Recruitment details:

This study was conducted in the Europe, Asia, North America and Pacific regions. Participants were randomized at 246 sites (165 in Europe, 23 in Asia, 39 in North America, and 19 in the Pacific). The study was co-sponsored by Intergroupe Francophone du Myélome (IFM) (for sites in France, Switzerland, and Belgium) and Celgene Corporation.

### Pre-assignment

#### Screening details:

Participants were stratified at randomization by 1) age ( $\leq 75$  versus  $> 75$  years), 2) stage (International Staging System Stages I or II versus Stage III), and 3) country.

### Period 1

Period 1 title	Active Treatment Phase (Ph) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)

#### Arm description:

Participants  $\leq 75$  years old received 25 mg lenalidomide (R) administered by mouth (PO) on days 1 to 21 of each 28-day treatment (rx) cycle plus 40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity. Participants  $> 75$  years old received lenalidomide 25 mg PO on the same schedule and frequency plus 20 mg dexamethasone at (@) the same schedule. Participants with moderate renal insufficiency received 10-15 mg lenalidomide (R) PO on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity. Participants with severe renal insufficiency received 15 mg lenalidomide (R) PO every other day on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid CC-5013
Pharmaceutical forms	Capsule
Routes of administration	Oral use

#### Dosage and administration details:

Lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day treatment cycle until disease progression. Subjects with moderate to severe renal insufficiency received 10-15 mg lenalidomide PO on days 1-21 of each 28-day treatment cycle.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

#### Dosage and administration details:

Dexamethasone 40 mg PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression. Those with moderate to severe renal insufficiency receive 20 - 40 mg PO on days 1, 8, 15, and 22 of a 28-day cycle

<b>Arm title</b>	Lenalidomide and Dexamethasone Rd18
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#### Arm description:

Participants  $\leq 75$  years old received 25 mg lenalidomide (R) PO on days 1 to 21 of each 28-day treatment cycle plus 40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to

18 cycles unless progressive disease (PD) or intolerable toxicity. Participants > 75 years old received lenalidomide 25 mg PO on the same schedule and frequency plus 20 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless PD or intolerable toxicity. Those with moderate renal insufficiency received 10-15 mg lenalidomide (R) PO on days 1-21 of each 28-day cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless PD or intolerable toxicity. Those with severe renal insufficiency received 15 mg lenalidomide (R) PO every other day (QOD) on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on the same schedule as above for up to 18 cycles until PD or intolerable toxicity.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	Revlimid, CC-5013
Pharmaceutical forms	Capsule
Routes of administration	Oral use

**Dosage and administration details:**

Lenalidomide 25 mg PO QD on days 1 to 21 of each 28-day treatment cycle for up to 18 cycles or until disease progression. Subjects with moderate to severe renal insufficiency received 10-15 mg lenalidomide PO on days 1-21 of each 28-day treatment cycle.

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Pharmaceutical forms	Tablet, Tablet
Routes of administration	Oral use, Oral use

**Dosage and administration details:**

Dexamethasone 40 mg PO on days 1, 8, 15, and 22 of a 28-day cycle. Those with moderate to severe renal insufficiency receive 20 - 40 mg PO on days 1, 8, 15, and 22 of a 28-day cycle up to 18 cycles or until disease progression.

<b>Arm title</b>	Melphalan + Prednisone + Thalidomide (MPT)
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**Arm description:**

Participants received melphalan (M) 0.25 mg/kg PO daily (QD) on days 1 to 4 of each 42-day cycle plus prednisone (P) at 2 mg/kg PO on days 1 to 4 of each 42-day cycle and thalidomide 200 mg PO QD on days 1 to 41 of each 42-day cycle. MPT therapy was given for up to 12 cycles unless PD or intolerable toxicity. Participants with moderate to severe renal insufficiency received melphalan (M) 0.10-0.125 mg/kg PO daily (QD) on days 1 to 4 of each 42-day cycle plus prednisone (P) at 2 mg/kg PO on days 1 to 4 of each 42-day cycle and thalidomide 100-200 mg PO QD on days 1 to 41 of each 42-day cycle. MPT therapy was given for up to 12 cycles unless PD or intolerable toxicity.

Arm type	Active comparator
Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran, L-PAM, L-Sarcylisin, Phenylalanine Mustard
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Melphalan 0.25 mg/kg PO QD on days 1 to 4 of each 42-day cycle up to 12 cycles or until disease progression.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	Deltasone, Orasone, Adasone, Deltacortisone, Prednisonum
Pharmaceutical forms	Tablet
Routes of administration	Oral use

**Dosage and administration details:**

Prednisone 2 mg/kg PO on days 1 to 4 of each 42-day cycle up to 12 cycles or until disease progression.

Investigational medicinal product name	Thalidomide
Investigational medicinal product code	
Other name	Thalomid, Immunoprin, Talidex, Talizer, Neurosedyn
Pharmaceutical forms	Capsule

Routes of administration	Oral use
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Dosage and administration details:

Thalidomide 200 mg PO QD on days 1 to 41 of each 42-day cycle for up to 12 cycles or disease progression.

Number of subjects in period 1	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)
Started	535	541	547
Safety Population	532	540	541
Untreated	3	1	6
Completed	0	0	0
Not completed	535	541	547
Adverse event, serious fatal	60	28	37
Study Close Out	64	26	21
Consent withdrawn by subject	16	16	21
Adverse event, non-fatal	68	71	76
Miscellaneous	52	34	47
Lost to follow-up	-	2	2
Disease Progression	273	362	339
Protocol deviation	2	2	4

## Baseline characteristics

### Reporting groups

Reporting group title	Lenalidomide and Low-Dose Dexamethasone (Rd)
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Reporting group description:

Participants ≤ 75 years old received 25 mg lenalidomide (R) administered by mouth (PO) on days 1 to 21 of each 28-day treatment (rx) cycle plus 40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity. Participants > 75 years old received lenalidomide 25 mg PO on the same schedule and frequency plus 20 mg dexamethasone at (@) the same schedule. Participants with moderate renal insufficiency received 10-15 mg lenalidomide (R) PO on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity. Participants with severe renal insufficiency received 15 mg lenalidomide (R) PO every other day on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity.

Reporting group title	Lenalidomide and Dexamethasone Rd18
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Reporting group description:

Participants ≤ 75 years old received 25 mg lenalidomide (R) PO on days 1 to 21 of each 28-day treatment cycle plus 40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless progressive disease (PD) or intolerable toxicity. Participants > 75 years old received lenalidomide 25 mg PO on the same schedule and frequency plus 20 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless PD or intolerable toxicity. Those with moderate renal insufficiency received 10-15 mg lenalidomide (R) PO on days 1-21 of each 28-day cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless PD or intolerable toxicity. Those with severe renal insufficiency received 15 mg lenalidomide (R) PO every other day (QOD) on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on the same schedule as above for up to 18 cycles until PD or intolerable toxicity.

Reporting group title	Melphalan + Prednisone + Thalidomide (MPT)
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Reporting group description:

Participants received melphalan (M) 0.25 mg/kg PO daily (QD) on days 1 to 4 of each 42-day cycle plus prednisone (P) at 2 mg/kg PO on days 1 to 4 of each 42-day cycle and thalidomide 200 mg PO QD on days 1 to 41 of each 42-day cycle. MPT therapy was given for up to 12 cycles unless PD or intolerable toxicity. Participants with moderate to severe renal insufficiency received melphalan (M) 0.10-0.125 mg/kg PO daily (QD) on days 1 to 4 of each 42-day cycle plus prednisone (P) at 2 mg/kg PO on days 1 to 4 of each 42-day cycle and thalidomide 100-200 mg PO QD on days 1 to 41 of each 42-day cycle. MPT therapy was given for up to 12 cycles unless PD or intolerable toxicity.

Reporting group values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects	535	541	547
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	73.2 ± 6.57	72.9 ± 6.5	73.1 ± 6.32
Gender, Male/Female Units: Subjects			
Female	241	268	260
Male	294	273	287
Race/Ethnicity, Customized Units: Subjects			
Asian	40	43	44

Black or African American	9	6	5
Native Hawaiian or other Pacific Islanders	1	0	1
White or Caucasian	474	480	491
Other, Miscellaneous	6	11	3
Missing	5	1	3
International Staging System (ISS)			
International Staging System (ISS): ISS is used as a staging system for multiple myeloma and divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Higher stages represent more advanced disease.			
Units: Subjects			
Stage I	106	106	103
Stage II	227	229	225
Stage III	202	206	219
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used to assess the progress of disease in a patient, how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.			
Units: Subjects			
0 (fully active)	155	163	156
1 (restrictive but ambulatory)	257	263	275
2 (ambulatory but unable to work)	119	113	111
3-4 (limited self-care, completely disabled)	2	2	2
Missing	2	0	3
Creatinine clearance			
Units: Subjects			
>=60 ml/min	269	280	285
<60 ml/min	266	261	261
Missing	0	0	1
Beta2 Microglobulin			
Units: Subjects			
>5.5 mg/L	224	224	234
<=5.5 mg/L	309	316	312
Missing	2	1	1
Albumin			
Units: Subjects			
<=35 g/L	192	209	223
> 35 g/L	343	331	324
Missing	0	1	0
Lactic Dehydrogenase			
Units: Subjects			
<200 U/L	448	442	434
>=200 U/L	86	99	112
Missing	1	0	1
Multiple Myeloma Subtype			
Units: Subjects			
Immunoglobulin A	138	142	123
Immunoglobulin A and Immunoglobulin G	7	6	8
Immunoglobulin A and Immunoglobulin M	0	0	1
Immunoglobulin D	4	7	4



Immunoglobulin G	334	331	350
Immunoglobulin M	3	1	1
Not available (includes light-chain disease)	49	54	60
Cytogenetic Risk			
Cytogenetic risk categories are mutually exclusive. Definitions: Adverse risk category: t(4:14), t(14:16), del (13q) or monosomy 13, del (17p), 1q gain; Non-adverse risk categories include favorable hyperdiploidy: t(11:14), gains of 5/9/15; normal: a normal result, gains other than 5/9/15, IgH deletion, and uncertain risk: probes used for analysis cannot place participant in any risk categories. Not evaluable: no specimen received, test failure or insufficient number of cells available for analysis.			
Units: Subjects			
Adverse Risk	170	185	189
Favorable Hyperdiploidy	112	103	102
Normal	148	131	141
Uncertain Risk	38	56	40
Not evaluable	34	35	44
Missing	33	31	31

<b>Reporting group values</b>	Total		
Number of subjects	1623		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	769		
Male	854		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	127		
Black or African American	20		
Native Hawaiian or other Pacific Islanders	2		
White or Caucasian	1445		
Other, Miscellaneous	20		
Missing	9		
International Staging System (ISS)			
International Staging System (ISS): ISS is used as a staging system for multiple myeloma and divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Higher stages represent more advanced disease.			
Units: Subjects			
Stage I	315		
Stage II	681		
Stage III	627		
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status is used to assess the progress of disease in a patient, how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.			
Units: Subjects			

0 (fully active)	474		
1 (restrictive but ambulatory)	795		
2 (ambulatory but unable to work)	343		
3-4 (limited self-care, completely disabled)	6		
Missing	5		
Creatinine clearance			
Units: Subjects			
>=60 ml/min	834		
<60 ml/min	788		
Missing	1		
Beta2 Microglobulin			
Units: Subjects			
>5.5 mg/L	682		
<=5.5 mg/L	937		
Missing	4		
Albumin			
Units: Subjects			
<=35 g/L	624		
> 35 g/L	998		
Missing	1		
Lactic Dehydrogenase			
Units: Subjects			
<200 U/L	1324		
>=200 U/L	297		
Missing	2		
Multiple Myeloma Subtype			
Units: Subjects			
Immunoglobulin A	403		
Immunoglobulin A and Immunoglobulin G	21		
Immunoglobulin A and Immunoglobulin M	1		
Immunoglobulin D	15		
Immunoglobulin G	1015		
Immunoglobulin M	5		
Not available (includes light-chain disease)	163		
Cytogenetic Risk			
Cytogenetic risk categories are mutually exclusive. Definitions: Adverse risk category: t(4:14), t(14:16), del (13q) or monosomy 13, del (17p), 1q gain; Non-adverse risk categories include favorable hyperdiploidy: t(11:14), gains of 5/9/15; normal: a normal result, gains other than 5/9/15, IgH deletion, and uncertain risk: probes used for analysis cannot place participant in any risk categories. Not evaluable: no specimen received, test failure or insufficient number of cells available for analysis.			
Units: Subjects			
Adverse Risk	544		
Favorable Hyperdiploidy	317		
Normal	420		
Uncertain Risk	134		
Not evaluable	113		
Missing	95		

## End points

### End points reporting groups

Reporting group title	Lenalidomide and Low-Dose Dexamethasone (Rd)
Reporting group description:	
Participants ≤ 75 years old received 25 mg lenalidomide (R) administered by mouth (PO) on days 1 to 21 of each 28-day treatment (rx) cycle plus 40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity. Participants > 75 years old received lenalidomide 25 mg PO on the same schedule and frequency plus 20 mg dexamethasone at (@) the same schedule. Participants with moderate renal insufficiency received 10-15 mg lenalidomide (R) PO on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity. Participants with severe renal insufficiency received 15 mg lenalidomide (R) PO every other day on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle until disease progression or intolerable toxicity.	
Reporting group title	Lenalidomide and Dexamethasone Rd18
Reporting group description:	
Participants ≤ 75 years old received 25 mg lenalidomide (R) PO on days 1 to 21 of each 28-day treatment cycle plus 40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless progressive disease (PD) or intolerable toxicity. Participants > 75 years old received lenalidomide 25 mg PO on the same schedule and frequency plus 20 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless PD or intolerable toxicity. Those with moderate renal insufficiency received 10-15 mg lenalidomide (R) PO on days 1-21 of each 28-day cycle and 20-40 mg dexamethasone (d) PO on days 1, 8, 15, and 22 of a 28-day cycle for up to 18 cycles unless PD or intolerable toxicity. Those with severe renal insufficiency received 15 mg lenalidomide (R) PO every other day (QOD) on days 1-21 of each 28-day treatment cycle and 20-40 mg dexamethasone (d) PO on the same schedule as above for up to 18 cycles until PD or intolerable toxicity.	
Reporting group title	Melphalan + Prednisone + Thalidomide (MPT)
Reporting group description:	
Participants received melphalan (M) 0.25 mg/kg PO daily (QD) on days 1 to 4 of each 42-day cycle plus prednisone (P) at 2 mg/kg PO on days 1 to 4 of each 42-day cycle and thalidomide 200 mg PO QD on days 1 to 41 of each 42-day cycle. MPT therapy was given for up to 12 cycles unless PD or intolerable toxicity. Participants with moderate to severe renal insufficiency received melphalan (M) 0.10-0.125 mg/kg PO daily (QD) on days 1 to 4 of each 42-day cycle plus prednisone (P) at 2 mg/kg PO on days 1 to 4 of each 42-day cycle and thalidomide 100-200 mg PO QD on days 1 to 41 of each 42-day cycle. MPT therapy was given for up to 12 cycles unless PD or intolerable toxicity.	

### Primary: Kaplan-Meier Estimates of Progression-free survival (PFS) Based on the Response Assessment by the Independent Review Adjudication Committee (IRAC)

End point title	Kaplan-Meier Estimates of Progression-free survival (PFS) Based on the Response Assessment by the Independent Review Adjudication Committee (IRAC)
End point description:	
PFS was calculated as the time from randomization to the 1st documented PD or death due to any cause during the study, which ever occurred first based on the International Myeloma Working Group Uniform Response criteria (IMWG). Those who withdrew for any reason or received another anti-myeloma therapy (AMT) without documented PD were censored on the date of their last response assessment, prior to receiving other AMT. Censoring PFS rules: - No baseline assessments and no progression or death documented within the 2 scheduled assessments; Death within the 1st two assessments without any response assessment; Progression documented between scheduled assessments; Death between assessments; no progression; study discontinuations for reasons other than PD or death; new AMT started prior to PD; death or PD after an extended lost to follow-up time period (2 or more missed scheduled assessment's). Intent to Treat population = subjects who were randomized even if no study drug was given.	
End point type	Primary
End point timeframe:	
From date of randomization until the data cut-off date of 24 May 2013. Median follow-up time for all participants was 17.1 months.	

<b>End point values</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: months				
median (confidence interval 95%)	25.5 (20.7 to 29.4)	20.7 (19.4 to 22)	21.2 (19.3 to 23.2)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Melphalan + Prednisone + Thalidomide (MPT) v Lenalidomide and Low-Dose Dexamethasone (Rd)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00006 <sup>[1]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.85

Notes:

[1] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00001 <sup>[2]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.82

Notes:

[2] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
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Statistical analysis description:

Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.70349 <sup>[3]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.2

Notes:

[3] - The p-value is based on the unstratified log-rank test.

### **Primary: Kaplan-Meier Estimates of PFS Based on the Response Assessment by the Investigator Assessment at the Time of Final Analysis**

End point title	Kaplan-Meier Estimates of PFS Based on the Response Assessment by the Investigator Assessment at the Time of Final Analysis
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End point description:

PFS was calculated as the time from randomization to the 1st documented PD or death due to any cause during the study, which ever occurred first based on the International Myeloma Working Group Uniform Response criteria (IMWG). Those who withdrew for any reason or received another anti-myeloma therapy (AMT) without documented PD were censored on the date of their last response assessment, prior to receiving other AMT. Censoring PFS rules: - No baseline assessments and no progression or death documented within the 2 scheduled assessments; Death within the 1st two assessments without any response assessment; Progression documented between scheduled assessments; Death between assessments; no progression; study discontinuations for reasons other than PD or death; new AMT started prior to PD; death or PD after an extended lost to follow-up time period (2 or more missed scheduled assessment's). Intent to Treat population = subjects who were randomized even if no study drug was given.

End point type	Primary
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End point timeframe:

From date of randomization to date of data cut-off date of 21 January 2016; median follow-up for all subjects was 17.7 months

<b>End point values</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: months				
median (confidence interval 95%)	26 (20.7 to 29.7)	21 (19.7 to 22.4)	21.9 (19.8 to 23.9)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description:	
Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[4]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.79

Notes:

[4] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description:	
Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[5]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	0.81

Notes:

[5] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91161 <sup>[6]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.14

Notes:

[6] - The p-value is based on the unstratified log-rank test.

### Secondary: Kaplan Meier Estimates of Overall Survival (OS) at the Time of Final Analysis

End point title	Kaplan Meier Estimates of Overall Survival (OS) at the Time of Final Analysis
End point description: Overall survival 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. All 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 the participant was known to be alive. ITT population (ITT) = all subjects who were randomized, independent of whether they received study treatment or not.	
End point type	Secondary
End point timeframe: From date of randomization to date of data cut-off of 21 January 2016; median follow-up for all subjects was 48.3 months	

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: months				
median (confidence interval 95%)	59.1 (53.9 to 65.9)	62.3 (53.6 to 68.7)	49.1 (44.3 to 53.5)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00234 <sup>[7]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.92

Notes:

[7] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82903 <sup>[8]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.2



Notes:

[8] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00119 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.9

Notes:

[9] - The p-value is based on the unstratified log-rank test.

### Secondary: Percentage of Participants With an Objective Response based on IRAC Review

End point title	Percentage of Participants With an Objective Response based on IRAC Review
End point description: Objective response according to IMWG Uniform Response Criteria was defined as a best overall response including a complete response (CR), very good partial response (VGPR) or partial response (PR) based on the IRAC Review. A CR is defined as: negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein and urine M-protein level $<100$ mg/24 hours; A PR is: $\geq 50\%$ reduction of serum M-Protein and reduction in urinary M-protein by $\geq 90\%$ or to $<200$ mg/24 hours. If present at baseline a $\geq 50\%$ reduction in size of soft tissue plasmacytomas. The ITT population includes all subjects who were randomized, independent of whether they received study treatment or not.	
End point type	Secondary
End point timeframe: Disease response was assessed every 28 days until the end of treatment or the data cut-off date of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.	

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: percentage of participants				

number (not applicable)	75.1	73.4	62.3	
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## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.41
upper limit	2.37

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53065
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.44

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)

Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	2.15

## Secondary: Percentage of Participants With an Objective Response based on Investigator Assessment at the Time of Final Analysis

End point title	Percentage of Participants With an Objective Response based on Investigator Assessment at the Time of Final Analysis
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### End point description:

Objective response according to IMWG Uniform Response Criteria was defined as a best overall response including a complete response (CR), very good partial response (VGPR) or partial response (PR) based on the IRAC Review. A CR is defined as: negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and  $\leq 5\%$  plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or  $\geq 90\%$  reduction in serum M-protein and urine M-protein level  $<100$  mg/24 hours; A PR is:  $\geq 50\%$  reduction of serum M-Protein and reduction in urinary M-protein by  $\geq 90\%$  or to  $<200$  mg/24 hours. If present at baseline a  $\geq 50\%$  reduction in size of soft tissue plasmacytomas. The ITT population includes all subjects who were randomized, independent of whether they received study treatment or not.

End point type	Secondary
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### End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 21 January 2016; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: percentage of participants				
number (not applicable)	80.7	78.6	67.5	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)

Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.53
upper limit	2.68

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.405
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.54

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00004
Method	Fisher exact
Parameter estimate	Log odds ratio
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.35
upper limit	2.32

## Secondary: Kaplan Meier estimates of duration of myeloma response as determined by the IRAC

End point title	Kaplan Meier estimates of duration of myeloma response as determined by the IRAC
End point description: Duration of response was defined as the duration from the time when the response criteria were first met for CR or VGPR or PR based on IMWG criteria until the first date the response criteria were met for progressive disease or until the participant died from any cause, whichever occurred first. Includes subjects with at least a partial response.	
End point type	Secondary
End point timeframe: Disease response was assessed every 28 days until end of treatment or the data cut-off date of 24 May 2013; median follow-up for responders was 20.1 months	

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	402	397	341	
Units: months				
median (confidence interval 95%)	35 (27.9 to 43.4)	22.1 (20.3 to 24)	22.3 (20.2 to 24.9)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[10]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.76

Notes:

[10] - The p-value is based on the unstratified log-rank test.

Statistical analysis title	Statistical Analysis 2
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**Statistical analysis description:**

Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[11]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.72

**Notes:**

[11] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
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**Statistical analysis description:**

Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7674 <sup>[12]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.23

**Notes:**

[12] - The p-value is based on the unstratified log-rank test.

**Secondary: Kaplan Meier estimates of duration of myeloma response as determined by an investigator assessment at the Time of Final Analysis**

End point title	Kaplan Meier estimates of duration of myeloma response as determined by an investigator assessment at the Time of Final Analysis
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**End point description:**

Duration of response was defined as the duration from the time when the response criteria were first met for CR or VGPR or PR based on IMWG criteria until the first date the response criteria were met for progressive disease or until the participant died from any cause, whichever occurred first. Includes subjects with at least a partial response.

End point type	Secondary
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End point timeframe:

Disease response was assessed every 28 days until end of treatment; data cut-off date of 21 January 2016; median follow-up for responders was 19.9 months.

<b>End point values</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	432	425	369	
Units: months				
median (confidence interval 95%)	31.5 (26.2 to 37.3)	21.5 (19.2 to 23)	22.1 (20.3 to 24.5)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
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Statistical analysis description:

Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[13]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.72

Notes:

[13] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 2
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Statistical analysis description:

Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
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Number of subjects included in analysis	857
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[14]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.72

Notes:

[14] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
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Statistical analysis description:

Hazard Ratio is based on stratified Cox proportional hazards model comparing the hazard functions associated with treatment groups.

Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	794
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99537 <sup>[15]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.17

Notes:

[15] - The p-value is based on the unstratified log-rank test.

## Secondary: Time to first response based on the review by the IRAC

End point title	Time to first response based on the review by the IRAC
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End point description:

The time to first myeloma 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 IMWG criteria. Includes subjects with at least a partial response.

End point type	Secondary
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End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm



<b>End point values</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	402	397	341	
Units: months				
median (full range (min-max))	1.8 (0.7 to 22.2)	1.8 (0.8 to 17.1)	2.8 (1.3 to 49.7)	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46672
Method	Wilcoxon (Mann-Whitney)

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	738
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

## Secondary: Time to first response based on the investigator assessment at the Time of Final Analysis

End point title	Time to first response based on the investigator assessment at the Time of Final Analysis
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**End point description:**

The time to first myeloma 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 IMWG criteria assessed by the investigator. Includes subjects with at least a partial response.

End point type	Secondary
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**End point timeframe:**

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 21 January 2016; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	430	425	368	
Units: months				
median (full range (min-max))	1.8 (0.5 to 22.2)	1.8 (0.8 to 34.8)	2.8 (1.2 to 56.3)	

**Statistical analyses**

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	855
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46987
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)

Number of subjects included in analysis	793
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001
Method	Wilcoxon (Mann-Whitney)

## Secondary: Kaplan Meier Estimates of Time to Treatment Failure (TTF)

End point title	Kaplan Meier Estimates of Time to Treatment Failure (TTF)
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End point description:

TTF is defined as the time between the randomization and discontinuation of study treatment for any reason, including disease progression (determined by IRAC based on the IMWG response criteria), treatment toxicity, start of another anti-myeloma therapy (AMT) and death. Includes the ITT population = subjects who were randomized, independent of whether they received study treatment or not.

End point type	Secondary
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End point timeframe:

From date of randomization until the data cut-off of 24 May 2013; median follow up for all participants was 16.1 months.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: months				
median (confidence interval 95%)	16.9 (14.1 to 18.4)	17.2 (14.6 to 18.2)	14.1 (12 to 16.1)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Based on a stratified Cox proportional hazards model.

Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00012 <sup>[16]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.88

Notes:

[16] - The p-value is based on unstratified log-rank test.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Based on a stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00187 <sup>[17]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.93

Notes:

[17] - The p-value is based on unstratified log-rank test.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Based on a stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45973 <sup>[18]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.08

Notes:

[18] - The p-value is based on unstratified log-rank test.

## Secondary: Kaplan Meier Estimates of Time to Treatment Failure (TTF) at the Time of Final Analysis

End point title	Kaplan Meier Estimates of Time to Treatment Failure (TTF) at the Time of Final Analysis
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End point description:

Time to treatment failure (TTF) is defined as the time between the randomization and discontinuation of study treatment for any reason, including disease progression (determined by the investigators assessment based on the IMWG response criteria), treatment toxicity, start of another anti-myeloma therapy (AMT), and death. ITT population = subjects who were randomized, independent of whether

they received study treatment or not.

End point type	Secondary
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End point timeframe:

From date of randomization until the date of the data cut-off of 21 January 2016; median follow up for all participants was 16.1 months.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: months				
median (confidence interval 95%)	16.9 (14.1 to 18.4)	17.2 (14.6 to 18.2)	14.1 (12 to 16.1)	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Hazard Ratio is based on stratified Cox proportional hazards model.

Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00002 <sup>[19]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.86

Notes:

[19] - The p-value is based on the unstratified log-rank test.

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Based on unstratified Cox proportional hazards model.

Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
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Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00126 <sup>[20]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.92

Notes:

[20] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description:	
Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27704 <sup>[21]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.06

Notes:

[21] - The p-value is based on the unstratified log-rank test.

### **Secondary: Kaplan Meier Estimates for time to second-line anti-myeloma treatment (AMT)**

End point title	Kaplan Meier Estimates for time to second-line anti-myeloma treatment (AMT)
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End point description:

Time to second-line anti-myeloma therapy was defined as time from randomization to the start of another non-protocol anti-myeloma therapy. Includes ITT population.

End point type	Secondary
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End point timeframe:

From date of randomization until the data cut-off of 24 May 2013; median follow-up for all participants was 23.0 months

<b>End point values</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535 <sup>[22]</sup>	541	547	
Units: months				
median (confidence interval 95%)	39.1 (32.8 to 99999)	28.5 (26.9 to 30.4)	26.7 (24 to 29.9)	

Notes:

[22] - 99999 = Could not be estimated due to the low number of events at the time of analysis.

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[23]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.78

Notes:

[23] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 2
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority <sup>[24]</sup>
P-value	= 0.00067 <sup>[25]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.88

Notes:

[24] - Based on unstratified Cox proportional hazards model.

[25] - The p-value is based on the unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description:	
Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12333 [26]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.03

Notes:

[26] - The p-value is based on unstratified log-rank test.

## Secondary: Kaplan Meier Estimates for time to second-line AMT at the Time of Final Analysis

End point title	Kaplan Meier Estimates for time to second-line AMT at the Time of Final Analysis
End point description:	
Time to second-line anti-myeloma therapy was defined as time from randomization to the start of another non-protocol anti-myeloma therapy. Includes ITT population.	
End point type	Secondary
End point timeframe:	
From date of randomization until the date of the data cut-off of 21 January 2016; median follow-up for all participants was 23.0 months.	

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	535	541	547	
Units: months				
median (full range (min-max))	36.7 (31.9 to 45.2)	28.5 (26.9 to 30.4)	26.7 (24 to 29.1)	

## Statistical analyses



<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	1082
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.00001 <sup>[27]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.73

Notes:

[27] - The p-value is based on unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	1076
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00001 <sup>[28]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.83

Notes:

[28] - The p-value is based on unstratified log-rank test.

<b>Statistical analysis title</b>	Statistical Analysis 3
Statistical analysis description: Hazard Ratio is based on stratified Cox proportional hazards model.	
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)

Number of subjects included in analysis	1088
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05821 [29]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1

Notes:

[29] - The p-value is based on unstratified log-rank test.

### Secondary: Percentage of Participants with a myeloma response by adverse risk cytogenetic risk category based on IRAC review

End point title	Percentage of Participants with a myeloma response by adverse risk cytogenetic risk category based on IRAC review
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End point description:

Participants were placed in adverse and non-adverse cytogenetic risk categories at baseline and response rates evaluated. Adverse Risk: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain Favorable Hyperdiploidy: : t(11;14), gains of 5/9/15; Normal: a normal result, gains other than 5/9/15, IgH deletion Uncertain risk: probes used for analysis cannot place those in any of the other risk categories. Objective response = best overall response including CR, VGPR or PR; A CR is negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein and urine M-protein level <100 mg/24 hours; A PR is ≥50% reduction of serum M-Protein and in urinary M-protein by ≥90% or to <200 mg/24 hours. If present at baseline a ≥50% reduction in size of soft tissue plasmacytomas. ITT with cytogenetic adverse risk.

End point type	Secondary
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End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	185	189	
Units: percentage of participants				
number (not applicable)	70	69.7	58.2	

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02134
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.59

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.59

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	374
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02374
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.53

## Secondary: Percentage of participants with a myeloma response by favorable hyperdiploidy risk cytogenetic risk category based on IRAC Review

End point title	Percentage of participants with a myeloma response by favorable hyperdiploidy risk cytogenetic risk category based on IRAC Review
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### End point description:

Participants were placed in adverse and non-adverse cytogenetic risk categories at baseline and response rates evaluated. Adverse Risk: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain. Favorable Hyperdiploidy: : t(11;14), gains of 5/9/15; Normal: a normal result, gains other than 5/9/15, IgH deletion. Uncertain risk: probes used for analysis cannot place participant in any of the other risk categories. Objective response = best overall response including CR, VGPR or PR; A CR is negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and  $\leq 5\%$  plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or  $\geq 90\%$  reduction in serum M-protein and urine M-protein level  $< 100$  mg/24 hours; A PR is  $\geq 50\%$  reduction of serum M-Protein and urinary M-protein by  $\geq 90\%$  or to  $< 200$  mg/24 hours. If present at baseline a  $\geq 50\%$  reduction in size of soft tissue plasmacytomas. ITT with favorable hyperdiploidy risk

End point type	Secondary
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### End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	112	103	102	
Units: percentage of participants				
number (not applicable)	80.4	81.6	70.6	

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11152
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	3.21

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86336
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.83

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07321
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	3.55

### **Secondary: Percentage of participants with a myeloma response by normal risk cytogenetic risk category based on IRAC Review**

End point title	Percentage of participants with a myeloma response by normal risk cytogenetic risk category based on IRAC Review
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#### **End point description:**

Participants were placed in adverse and non-adverse cytogenetic risk categories at baseline and response rates evaluated. Adverse Risk: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain Favorable Hyperdiploidy: : t(11;14), gains of 5/9/15; Normal: a normal result, gains other than 5/9/15, IgH deletion Uncertain risk: probes used for analysis cannot place participant in any of the other risk categories. Objective response = best overall response including CR, VGPR or PR; A CR is negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein and urine M-protein level <100 mg/24 hours; A PR is ≥50% reduction of serum M-Protein and urinary M-protein by ≥90% or to <200 mg/24 hours. If

present at baseline a  $\geq 50\%$  reduction in size of soft tissue plasmacytomas. ITT population with normal risk.

End point type	Secondary
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End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	148	131	141	
Units: percentage of participants				
number (not applicable)	80.4	74.8	61	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00043
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.55
upper limit	4.45

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31274
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	2.43

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01936
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	3.19

### **Secondary: Percentage of participants with a myeloma response by uncertain risk cytogenetic risk category based on IRAC Review**

End point title	Percentage of participants with a myeloma response by uncertain risk cytogenetic risk category based on IRAC Review
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#### End point description:

Participants were placed in adverse and non-adverse cytogenetic risk categories at baseline and response rates evaluated. Adverse Risk: t(4;14), t(14;16), del(13q) or monosomy 13, del(17p), 1q gain Favorable Hyperdiploidy: : t(11;14), gains of 5/9/15; Normal: a normal result, gains other than 5/9/15, IgH deletion Uncertain risk: probes used for analysis cannot place participant in any of the other risk categories. Objective response = best overall response including CR, VGPR or PR; A CR is negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein and urine M-protein level <100 mg/24 hours; A PR is ≥50% reduction of serum M-Protein and urinary M-protein by ≥90% or to <200 mg/24 hours. If present at baseline a ≥50% reduction in size of soft tissue plasmacytomas. ITT population with uncertain risk.

End point type	Secondary
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#### End point timeframe:

Disease response was assessed every 28 days until end of treatment or the data cut-off date of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm

<b>End point values</b>	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	56	40	
Units: percentage of participants				
number (not applicable)	60.5	76.8	57.5	

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82128
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2.8

<b>Statistical analysis title</b>	Statistical Analysis 2
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11041
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.14

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)



Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07302
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	5.91

### Secondary: Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer (EORTC QLQ-C30) Global Health Status Domain

End point title	Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer (EORTC QLQ-C30) Global Health Status Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Global Health Status/QOL scale is scored between 0 and 100, with a high score indicating better Global Health Status/QOL. Negative change from Baseline values indicate deterioration in QOL or functioning and positive values indicate improvement.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	508 <sup>[30]</sup>	507 <sup>[31]</sup>	508 <sup>[32]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	0.4 (± 23.98)	-1.3 (± 23.93)	1 (± 23.68)	
Month 3	4.8 (± 24.15)	4.7 (± 25.15)	4.3 (± 26.04)	
Month 6	5.9 (± 25.93)	5.4 (± 23.88)	6.1 (± 25.98)	
Month 12	4.8 (± 26.42)	3.2 (± 25.38)	6.5 (± 25.9)	
Month 18	6.4 (± 28.02)	5.7 (± 24.86)	4.8 (± 27.05)	
Study discontinuation	-0.1 (± 27.07)	5 (± 27.33)	0.3 (± 28.07)	

Notes:

[30] - Month 1 = 438

Month 3 = 421

Month 6 = 369

Month 12 = 302  
 Month 18 = 246  
 Discontinuation = 203

[31] - Month 1 = 441  
 Month 3 = 413  
 Month 6 = 376  
 Month 12 = 299  
 Month 18 = 238  
 Discontinuation = 261

[32] - Month 1 = 415  
 Month 3 = 396  
 Month 6 = 351  
 Month 12 = 252  
 Month 18 = 178  
 Discontinuation = 257

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Physical Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	511 <sup>[33]</sup>	514 <sup>[34]</sup>	509 <sup>[35]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	-1.7 (± 21.11)	-1.4 (± 19.56)	-0.9 (± 21.28)	
Month 3	3.4 (± 23.33)	4.7 (± 22.94)	2.2 (± 23.68)	
Month 6	4.7 (± 25.09)	7.6 (± 22.85)	5.3 (± 24.52)	
Month 12	5 (± 25.65)	7.4 (± 23.4)	6.9 (± 27.22)	
Month 18	6.9 (± 26.71)	6.8 (± 23.58)	8.3 (± 27.1)	
Discontinuation Visit	-0.1 (± 29.7)	3 (± 27.32)	-0.1 (± 27.58)	

Notes:

[33] - Month 1 = 445  
Month 3 = 426  
Month 6 = 376  
Month 12 = 307  
Month 18 = 247  
Discontinuation = 207

[34] - Month 1 = 449  
Month 3 = 421  
Month 6 = 382  
Month 12 = 302  
Month 18 = 243  
Discontinuation = 267  
[35] - Month 1 = 419  
Month 3 = 396  
Month 6 = 352  
Month 12 = 253  
Month 18 = 183  
Discontinuation = 256

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the EORTC QLQ-C30 Role Functioning Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Role Functioning Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Role Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509 <sup>[36]</sup>	508 <sup>[37]</sup>	508 <sup>[38]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	-2.7 (± 29.94)	-4.6 (± 28.2)	-2.4 (± 30.48)	
Month 3	2.4 (± 33.32)	6.3 (± 32.43)	4.1 (± 34.23)	
Month 6	6.3 (± 35.44)	8.6 (± 32.42)	8.2 (± 36.09)	
Month 12	7.8 (± 36.6)	9.4 (± 34.15)	11.8 (± 38.94)	
Month 18	8 (± 35.34)	9.1 (± 34.35)	14.5 (± 39.03)	
Discontinuation Visit	-0.3 (± 39.58)	3.8 (± 36.34)	-1 (± 38.41)	

Notes:

[36] - Month 1 = 442  
Month 3 = 422  
Month 6 = 373  
Month 12 = 305  
Month 18 = 245  
Discontinuation = 206

[37] - Month 1 = 445  
Month 3 = 419  
Month 6 = 378  
Month 12 = 300  
Month 18 = 240  
Discontinuation = 264

[38] - Month 1 = 415  
Month 3 = 395  
Month 6 = 352  
Month 12 = 252  
Month 18 = 182  
Discontinuation = 256

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Emotional Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1(Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509 <sup>[39]</sup>	510 <sup>[40]</sup>	510 <sup>[41]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	0.6 (± 22.13)	0.1 (± 20.73)	1 (± 21.52)	
Month 3	3.8 (± 22.29)	3.9 (± 22.11)	2.1 (± 22.27)	
Month 6	4.6 (± 24.36)	5.8 (± 22.39)	5.5 (± 22.55)	
Month 12	4.6 (± 24.08)	4.9 (± 22.23)	5.1 (± 22.37)	
Month 18	5.8 (± 25.61)	3.1 (± 23.31)	5.1 (± 22.99)	

Discontinuation Visit	2.6 ( $\pm$ 24.3)	3.7 ( $\pm$ 23.77)	0 ( $\pm$ 24.72)	
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Notes:

[39] - Month 1 = 443  
Month 3 = 423  
Month 6 = 375  
Month 12 = 305  
Month 18 = 246  
Discontinuation = 205

[40] - Month 1 = 446  
Month 3 = 415  
Month 6 = 379  
Month 12 = 301  
Month 18 = 242  
Discontinuation = 263

[41] - Month 1 = 419  
Month 3 = 397  
Month 6 = 351  
Month 12 = 254  
Month 18 = 179  
Discontinuation = 256

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Cognitive Functioning Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Cognitive Functioning Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Cognitive Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509 <sup>[42]</sup>	510 <sup>[43]</sup>	510 <sup>[44]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	-1.2 ( $\pm$ 21.73)	-1.7 ( $\pm$ 19.08)	-1.8 ( $\pm$ 24.07)	
Month 3	-0.7 ( $\pm$ 22.89)	1.8 ( $\pm$ 20.94)	-1.5 ( $\pm$ 24.02)	
Month 6	-0.9 ( $\pm$ 22.57)	0.9 ( $\pm$ 19.77)	-0.3 ( $\pm$ 23.55)	
Month 12	-1.6 ( $\pm$ 25.05)	-1.2 ( $\pm$ 20.19)	-0.6 ( $\pm$ 22.97)	
Month 18	-2.2 ( $\pm$ 25.61)	-2.8 ( $\pm$ 20.97)	-0.7 ( $\pm$ 23.99)	

Discontinuation Visit	-4.9 (± 27.57)	-2.6 (± 22.34)	-7.1 (± 25.15)	
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Notes:

[42] - Month 1 = 443  
Month 3 = 424  
Month 6 = 375  
Month 12 = 306  
Month 18 = 246  
Discontinuation = 206

[43] - Month 1 = 447  
Month 3 = 415  
Month 6 = 379  
Month 12 = 301  
Month 18 = 242  
Discontinuation = 263

[44] - Month 1 = 419  
Month 3 = 397  
Month 6 = 353  
Month 12 = 254  
Month 18 = 179  
Discontinuation = 256

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Social Functioning Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Social Functioning Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Social Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1(Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	505 <sup>[45]</sup>	503 <sup>[46]</sup>	503 <sup>[47]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	-4.3 (± 29.1)	-2.2 (± 27.44)	-1.4 (± 30.52)	
Month 3	0.7 (± 29.36)	2 (± 30.93)	2.4 (± 30.7)	
Month 6	4 (± 32.48)	5.2 (± 28.5)	3.4 (± 35.24)	
Month 12	2.9 (± 34.96)	3.8 (± 32.29)	5.8 (± 33.68)	
Month 18	4.2 (± 34.99)	3.2 (± 31.67)	6 (± 35.2)	
Discontinuation Visit	-1.2 (± 33.5)	2.7 (± 33.37)	-3.5 (± 33.2)	

Notes:

[45] - Month 1 = 439  
Month 3 = 419  
Month 6 = 374  
Month 12 = 305  
Month 18 = 247  
Discontinuation = 204

[46] - Month 1 = 441  
Month 3 = 410  
Month 6 = 374  
Month 12 = 298  
Month 18 = 239  
Discontinuation = 257

[47] - Month 1 = 414  
Month 3 = 389  
Month 6 = 348  
Month 12 = 252  
Month 18 = 177  
Discontinuation = 254

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the EORTC QLQ-C30 Fatigue Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Fatigue Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Fatigue Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate improvement in symptoms and positive values indicate worsening symptoms. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1(Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	511 <sup>[48]</sup>	514 <sup>[49]</sup>	512 <sup>[50]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	2.6 (± 25.32)	4.4 (± 24.03)	2.8 (± 25.44)	
Month 3	-2.5 (± 28.15)	-3.4 (± 25.16)	-1.8 (± 28.53)	
Month 6	-3.7 (± 28.54)	-5.9 (± 26.37)	-4.5 (± 29.09)	
Month 12	-4.3 (± 29.47)	-2.3 (± 26.63)	-3.9 (± 29.56)	
Month 18	-3.1 (± 29.82)	0.1 (± 29.12)	-4.3 (± 30.05)	
Discontinuation Visit	0.3 (± 29.75)	-1.6 (± 29.11)	2.7 (± 30.15)	

Notes:

[48] - Month 1 = 445  
Month 3 = 425  
Month 6 = 376  
Month 12 = 306  
Month 18 = 244  
Discontinuation = 207

[49] - Month 1 = 448  
Month 3 = 423  
Month 6 = 383  
Month 12 = 303  
Month 18 = 242  
Discontinuation = 267

[50] - Month 1 = 421  
Month 3 = 400  
Month 6 = 355  
Month 12 = 255  
Month 18 = 184  
Discontinuation = 258

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the EORTC QLQ-C30 Pain Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Pain Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Pain Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate improvement in symptoms and positive values indicate worsening symptoms. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	511 <sup>[51]</sup>	514 <sup>[52]</sup>	512 <sup>[53]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	-5.4 (± 31.89)	-4.4 (± 30.7)	-7.8 (± 30.93)	
Month 3	-13.4 (± 34.28)	-13.1 (± 32.32)	-12.1 (± 31.98)	
Month 6	-14.4 (± 35.64)	-16.1 (± 33.44)	-13.4 (± 34.45)	
Month 12	-14 (± 36.05)	-14.7 (± 32.34)	-14.3 (± 32.85)	



Month 18	-14.4 (± 35.03)	-12.4 (± 35.28)	-14.7 (± 32.81)	
Discontinuation Visit	-8 (± 39.37)	-7.9 (± 37.65)	-6 (± 37.09)	

Notes:

[51] - Month 1 = 446  
Month 3 = 426  
Month 6 = 379  
Month 12 = 306  
Month 18 = 248  
Discontinuation = 207

[52] - Month 1 = 453  
Month 3 = 423  
Month 6 = 384  
Month 12 = 304  
Month 18 = 242  
Discontinuation = 266

[53] - Month 1 = 423  
Month 3 = 399  
Month 6 = 355  
Month 12 = 255  
Month 18 = 183  
Discontinuation = 259

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Nausea/Vomiting Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Nausea/Vomiting Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Nausea/Vomiting Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate improvement in symptoms and positive values indicate worsening symptoms. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	511 <sup>[54]</sup>	513 <sup>[55]</sup>	512 <sup>[56]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	1.8 (± 20.05)	-0.5 (± 23.19)	4 (± 22.91)	
Month 3	-1.1 (± 19.42)	-2.5 (± 21.92)	-1.2 (± 19.89)	
Month 6	-1.3 (± 18.53)	-4 (± 21.52)	-3.9 (± 19.57)	
Month 12	-2.2 (± 17.16)	-3.6 (± 18.86)	-3.9 (± 19.09)	

Month 18	-2.3 (± 19.2)	-2.7 (± 18.92)	-3.9 (± 19.44)	
Discontinuation Visit	0.4 (± 21.43)	-4.2 (± 24.37)	1 (± 21.46)	

Notes:

[54] - Month 1 = 446  
Month 3 = 426  
Month 6 = 377  
Month 12 = 306  
Month 18 = 246  
Discontinuation = 206

[55] - Month 1 = 449  
Month 3 = 422  
Month 6 = 381  
Month 12 = 302  
Month 18 = 242  
Discontinuation = 267

[56] - Month 1 = 424  
Month 3 = 399  
Month 6 = 355  
Month 12 = 255  
Month 18 = 184  
Discontinuation = 258

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Dyspnea Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Dyspnea Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Dyspnoea Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate improvement in symptoms and positive values indicate worsening symptoms. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1(Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509 <sup>[57]</sup>	508 <sup>[58]</sup>	506 <sup>[59]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	0.9 (± 30.87)	3.6 (± 29.85)	4.2 (± 32.04)	
Month 3	-0.8 (± 31.87)	-1.9 (± 29.45)	2 (± 32.49)	
Month 6	-2.3 (± 33.12)	-2.9 (± 29.66)	0.1 (± 30.29)	
Month 12	-3.5 (± 30.97)	-1.6 (± 29.23)	-1.6 (± 32.76)	

Month 18	-1.8 (± 32.73)	2.9 (± 28.33)	0.4 (± 32.68)	
Discontinuation Visit	-1 (± 37.42)	0.8 (± 31.01)	7.8 (± 33.72)	

Notes:

[57] - Month 1 = 439  
Month 3 = 423  
Month 6 = 372  
Month 12 = 303  
Month 18 = 244  
Discontinuation = 204

[58] - Month 1 = 440  
Month 3 = 417  
Month 6 = 375  
Month 12 = 294  
Month 18 = 238  
Discontinuation = 262

[59] - Month 1 = 417  
Month 3 = 390  
Month 6 = 351  
Month 12 = 253  
Month 18 = 182  
Discontinuation = 255

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Insomnia Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Insomnia Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Insomnia Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate improvement in symptoms and positive values indicate worsening symptoms. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	510 <sup>[60]</sup>	513 <sup>[61]</sup>	511 <sup>[62]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	2.1 (± 33.34)	3.2 (± 34.32)	-10.5 (± 30.47)	
Month 3	0.2 (± 35.11)	-1.3 (± 33.54)	-8.9 (± 35.28)	

Month 6	-1.2 (± 34.84)	-1.9 (± 31.43)	-11.6 (± 32.96)	
Month 12	-1 (± 34.78)	1.1 (± 32.47)	-9.6 (± 31)	
Month 18	-0.5 (± 37.11)	1.4 (± 35.72)	-6 (± 34.42)	
Discontinuation Visit	-5.2 (± 36.47)	-1.6 (± 31.27)	-4.5 (± 36.98)	

Notes:

[60] - Month 1 = 443

Month 3 = 422

Month 6 = 374

Month 12 = 303

Month 18 = 243

Discontinuation = 204

[61] - Month 1 = 447

Month 3 = 420

Month 6 = 382

Month 12 = 300

Month 18 = 241

Discontinuation = 265

[62] - Month 1 = 421

Month 3 = 399

Month 6 = 353

Month 12 = 253

Month 18 = 182

Discontinuation = 254

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Appetite Loss Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Appetite Loss Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Appetite Loss Scale is scored between 0 and 100, with a high score indicating a higher level of appetite loss. Negative change from Baseline values indicate improvement in appetite and positive values indicate worsening of appetite.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509 <sup>[63]</sup>	512 <sup>[64]</sup>	510 <sup>[65]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	1.3 (± 33.46)	2.9 (± 31.87)	1 (± 32.35)	
Month 3	-5.9 (± 38.34)	-3.3 (± 35.25)	-6.2 (± 35.03)	

Month 6	-9.8 (± 40.02)	-8.6 (± 33.98)	-13.5 (± 35.98)	
Month 12	-7.3 (± 37.07)	-6.4 (± 35.3)	-10.5 (± 34.16)	
Month 18	-8.1 (± 35.97)	-5.1 (± 33.29)	-12.2 (± 31.88)	
Discontinuation Visit	-1 (± 36.77)	-7.5 (± 37.49)	-2.6 (± 37.18)	

Notes:

[63] - Month 1 = 442  
Month 3 = 424  
Month 6 = 374  
Month 12 = 307  
Month 18 = 246  
Discontinuation = 203

[64] - Month 1 = 447  
Month 3 = 421  
Month 6 = 381  
Month 12 = 299  
Month 18 = 241  
Discontinuation = 267

[65] - Month 1 = 422  
Month 3 = 396  
Month 6 = 354  
Month 12 = 253  
Month 18 = 183  
Discontinuation = 257

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Constipation Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Constipation Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Constipation Scale is scored between 0 and 100, with a high score indicating a higher level of constipation. Negative change from Baseline values indicate improvement in constipation and positive values indicate worsening of constipation.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	508 <sup>[66]</sup>	511 <sup>[67]</sup>	510 <sup>[68]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	8.3 (± 36.74)	6.3 (± 36.18)	18.4 (± 41.23)	

Month 3	1.8 (± 37.53)	0 (± 37.02)	13.9 (± 39.3)	
Month 6	-2.4 (± 37.51)	-5.1 (± 37.39)	6.8 (± 40.41)	
Month 12	-2.4 (± 38.79)	-5.2 (± 38.09)	3.7 (± 38.28)	
Month 18	-4.5 (± 35.42)	-5.9 (± 36.65)	0 (± 37.06)	
Discontinuation Visit	-7.9 (± 39.98)	-7.5 (± 39.2)	-2.2 (± 38.86)	

Notes:

[66] - Month 1 = 441  
Month 3 = 422  
Month 6 = 373  
Month 12 = 304  
Month 18 = 246  
Discontinuation = 203

[67] - Month 1 = 446  
Month 3 = 416  
Month 6 = 377  
Month 12 = 301  
Month 18 = 242  
Discontinuation = 261

[68] - Month 1 = 419  
Month 3 = 397  
Month 6 = 353  
Month 12 = 255  
Month 18 = 179  
Discontinuation = 257

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Diarrhea Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Diarrhea Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Diarrhea Scale is scored between 0 and 100, with a high score indicating a higher level of diarrhea. Negative change from Baseline values indicate improvement in diarrhea and positive values indicate worsening of diarrhea. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	508 <sup>[69]</sup>	509 <sup>[70]</sup>	510 <sup>[71]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	3.8 (± 25.53)	2.3 (± 24.94)	-0.6 (± 18.79)	

Month 3	3.7 (± 24.99)	3.4 (± 27.27)	-2.4 (± 18.61)	
Month 6	8.2 (± 28.36)	6 (± 27.95)	-2.2 (± 21.19)	
Month 12	11.8 (± 31.35)	9.1 (± 28.74)	-2.5 (± 17.26)	
Month 18	14.8 (± 31.2)	10.9 (± 30.96)	-1.7 (± 17.46)	
Discontinuation Visit	10.8 (± 29.56)	6.4 (± 31.38)	-0.5 (± 19.39)	

Notes:

[69] - Month 1 = 438  
Month 3 = 419  
Month 6 = 373  
Month 12 = 303  
Month 18 = 246  
Discontinuation = 206

[70] - Month 1 = 444  
Month 3 = 413  
Month 6 = 376  
Month 12 = 299  
Month 18 = 241  
Discontinuation = 261

[71] - Month 1 = 416  
Month 3 = 395  
Month 6 = 351  
Month 12 = 253  
Month 18 = 178  
Discontinuation = 255

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the EORTC QLQ-C30 Financial Difficulties Domain

End point title	Change From Baseline in the EORTC QLQ-C30 Financial Difficulties Domain
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End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Financial Difficulties Scale is scored between 0 and 100, with a high score indicating a higher level of financial difficulties. Negative change from Baseline values indicate improvement in financial difficulties and positive values indicate worsening of financial difficulties. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	501 <sup>[72]</sup>	504 <sup>[73]</sup>	502 <sup>[74]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				

Month 1	2.1 (± 21.43)	-0.3 (± 20.59)	0.5 (± 22.98)	
Month 3	1.9 (± 23.09)	-0.4 (± 21.88)	1.9 (± 21.48)	
Month 6	1.4 (± 22.92)	-0.3 (± 21.24)	0.7 (± 24.57)	
Month 12	0.4 (± 23.99)	1.6 (± 23.28)	1.1 (± 23.16)	
Month 18	2 (± 22.23)	1.8 (± 23.3)	0.4 (± 21.2)	
Discontinuation Visit	1.9 (± 27.19)	0.5 (± 23.84)	5 (± 24.82)	

Notes:

[72] - Month 1 = 435  
Month 3 = 413  
Month 6 = 370  
Month 12 = 302  
Month 18 = 244  
Discontinuation = 197

[73] - Month 1 = 441  
Month 3 = 407  
Month 6 = 373  
Month 12 = 299  
Month 18 = 239  
Discontinuation = 255

[74] - Month 1 = 409  
Month 3 = 388  
Month 6 = 345  
Month 12 = 249  
Month 18 = 174  
Discontinuation = 254

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the 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 in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms Scale
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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). Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	510 <sup>[75]</sup>	512 <sup>[76]</sup>	511 <sup>[77]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				



Month 1	-4 (± 18.75)	-4.1 (± 19.37)	-4.4 (± 19.04)	
Month 3	-9.1 (± 21.66)	-10 (± 19.97)	-7 (± 20.43)	
Month 6	-8.8 (± 20.89)	-9.9 (± 20.94)	-7.9 (± 21.94)	
Month 12	-7.8 (± 21.74)	-8.7 (± 20.29)	-6.5 (± 21.58)	
Month 18	-8.7 (± 23.5)	-6.2 (± 23.3)	-7.9 (± 21.26)	
Discontinuation Visit	-3.5 (± 24.82)	-4.5 (± 24.9)	-3.7 (± 23.54)	

Notes:

[75] - Month 1 = 442  
Month 3 = 422  
Month 6 = 375  
Month 12 = 306  
Month 18 = 249  
Discontinuation = 205

[76] - Month 1 = 448  
Month 3 = 418  
Month 6 = 381  
Month 12 = 303  
Month 18 = 243  
Discontinuation = 266

[77] - Month 1 = 421  
Month 3 = 396  
Month 6 = 353  
Month 12 = 254  
Month 18 = 183  
Discontinuation = 259

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Side Effects Treatment Scale

End point title	Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Side Effects Treatment Scale
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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 represents a more severe overall side effect of treatment. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	509 <sup>[78]</sup>	511 <sup>[79]</sup>	510 <sup>[80]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				

Month 1	2.5 (± 13.72)	4 (± 14.89)	5.6 (± 15)	
Month 3	1 (± 15.23)	1.2 (± 14.67)	3.5 (± 15.4)	
Month 6	1.7 (± 15.58)	-0.4 (± 14.39)	2.9 (± 17.28)	
Month 12	1.9 (± 14.49)	1.2 (± 16.2)	4.7 (± 17.17)	
Month 18	2.2 (± 15.63)	2.3 (± 17.36)	4.3 (± 16.37)	
Discontinuation Visit	0.6 (± 15.85)	-1 (± 15.81)	3.8 (± 16.52)	

Notes:

[78] - Month 1 = 438

Month 3 = 421

Month 6 = 374

Month 12 = 305

Month 18 = 247

Discontinuation = 205

[79] - Month 1 = 446

Month 3 = 417

Month 6 = 378

Month 12 = 301

Month 18 = 243

Discontinuation = 262

[80] - Month 1 = 418

Month 3 = 393

Month 6 = 351

Month 12 = 254

Month 18 = 182

Discontinuation = 258

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Future Perspective Scale

End point title	Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Future Perspective Scale
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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; for the future perspective scale, a higher score indicates a better perspective of the future. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	504 <sup>[81]</sup>	508 <sup>[82]</sup>	509 <sup>[83]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	4.7 (± 22.17)	3.9 (± 20.94)	3.3 (± 23.2)	
Month 3	8.5 (± 23.28)	9.2 (± 22.95)	6.3 (± 25.06)	
Month 6	9.8 (± 23.67)	12.3 (± 24.84)	8 (± 25.26)	
Month 12	10.8 (± 21.9)	12.1 (± 24.41)	10 (± 26.3)	
Month 18	12.7 (± 23.96)	11.7 (± 24.76)	9.5 (± 21.75)	
Discontinuation Visit	5.8 (± 25.91)	8.8 (± 26.71)	3.2 (± 27.13)	

Notes:

[81] - Month 1 = 433  
Month 3 = 416  
Month 6 = 367  
Month 12 = 303  
Month 18 = 245  
Discontinuation = 203

[82] - Month 1 = 443  
Month 3 = 414  
Month 6 = 377  
Month 12 = 299  
Month 18 = 239  
Discontinuation = 264

[83] - Month 1 = 415  
Month 3 = 394  
Month 6 = 350  
Month 12 = 249  
Month 18 = 179  
Discontinuation = 254

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Body Image Scale

End point title	Change From Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Multiple Myeloma (EORTC QLQ-MY20) Body Image Scale
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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; for the body image scale, a higher score indicates a better body image. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	492 <sup>[84]</sup>	498 <sup>[85]</sup>	504 <sup>[86]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	-4.5 (± 29.44)	-1.5 (± 27.19)	-1.6 (± 29.97)	
Month 3	-1.7 (± 27.54)	0.8 (± 26.23)	-3 (± 29.38)	
Month 6	-1.4 (± 27.84)	1.5 (± 29.72)	-2.8 (± 33.07)	
Month 12	-1.4 (± 29.6)	-0.4 (± 31.64)	-2.6 (± 31.96)	
Month 18	-2.3 (± 28.09)	-0.3 (± 31.04)	-1.1 (± 33.6)	
Discontinuation Visit	-5.6 (± 34.29)	1.8 (± 30.66)	-5.6 (± 33.73)	

Notes:

[84] - Month 1 = 417  
Month 3 = 404  
Month 6 = 357  
Month 12 = 292  
Month 18 = 236  
Discontinuation = 197

[85] - Month 1 = 422  
Month 3 = 398  
Month 6 = 366  
Month 12 = 284  
Month 18 = 227  
Discontinuation = 253

[86] - Month 1 = 408  
Month 3 = 387  
Month 6 = 347  
Month 12 = 242  
Month 18 = 174  
Discontinuation = 250

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in the European Quality of Life-5 Dimensions (EQ-5D) Health Utility Index Score

End point title	Change From Baseline in the European Quality of Life-5 Dimensions (EQ-5D) Health Utility Index Score
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End point description:

EQ-5D is a self-administered questionnaire that assesses health-related quality of life. The EQ-5D descriptive health profile comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 3 levels of response: No problem (1), some problems (2), and extreme problems (3). A unique EQ-5D health state is defined by combining one level from each of the five dimensions into a single utility index score. EQ-5D index values range from -0.59 to 1.00 where higher EQ-5D scores represent better health status. A positive change from baseline score indicates improvement in health status and better health state. Includes the ITT population with available data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1 (Baseline), then Months 1, 3, 6, 12, 18 and Discontinuation visit

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	490 <sup>[87]</sup>	492 <sup>[88]</sup>	490 <sup>[89]</sup>	
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 1	0 (± 0.29)	0 (± 0.31)	0 (± 0.28)	
Month 3	0.1 (± 0.33)	0.1 (± 0.32)	0.1 (± 0.32)	
Month 6	0.1 (± 0.32)	0.1 (± 0.31)	0.1 (± 0.34)	
Month 12	0.1 (± 0.33)	0.1 (± 0.31)	0.1 (± 0.35)	
Month 18	0.1 (± 0.36)	0.1 (± 0.32)	0.1 (± 0.35)	
Discontinuation Visit	0 (± 0.4)	0 (± 0.35)	0 (± 0.39)	

Notes:

[87] - Month 1 = 400

Month 3 = 389

Month 6 = 341

Month 12 = 283

Month 18 = 219

Discontinuation = 186

[88] - Month 1 = 420

Month 3 = 383

Month 6 = 351

Month 12 = 278

Month 18 = 230

Discontinuation = 231

[89] - Month 1 = 381

Month 3 = 366

Month 6 = 323

Month 12 = 231

Month 18 = 170

Discontinuation = 240

## Statistical analyses

No statistical analyses for this end point

## Secondary: Healthcare Resource Utilization (HRU): Rate of Inpatient Hospitalizations Per Year

End point title	Healthcare Resource Utilization (HRU): Rate of Inpatient Hospitalizations Per Year
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End point description:

HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient. HRU Analysis may help in evaluating potential costs and budget impact of new treatments from a payer perspective. The rate of inpatient hospitalizations per patient year was calculated as the total number of hospitalizations divided by the total number of patient-years followed in the study period. Patient-years (PY) were calculated as the duration from baseline to last available HRQL assessment for each patient. HRU data not analyzed.

End point type	Secondary
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End point timeframe:

Day 1 (randomization) up to last visit completed 25 July 2016

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[90]</sup>	0 <sup>[91]</sup>	0 <sup>[92]</sup>	
Units: hospitalizations per patient year				
number (not applicable)				

Notes:

[90] - 0 = HRU data not analyzed.

[91] - 0 = HRU data not analyzed.

[92] - 0 = HRU data not analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Adverse Events (AEs) During the Active Treatment Phase

End point title	Number of Participants With Adverse Events (AEs) During the Active Treatment Phase
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End point description:

A treatment emergent adverse event (TEAE) is 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. 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 included all subjects who received at least one dose of treatment in any arm.

End point type	Secondary
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End point timeframe:

From first dose of study drug through 28 days following the discontinuation visit from active treatment phase; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	532	540	541	
Units: Participants				
≥ 1 adverse event (AE)	529	536	539	
≥ 1 grade (Gr) 3 or 4 AE	453	433	480	
≥ 1 grade (Gr) 5 AE	50	36	38	
≥ 1 serious adverse event (SAE)	359	308	270	
≥ 1 AE related to Len/Dex/MPT	506	501	527	
≥ 1 AE related to Lenalidomide	482	481	0	
≥ 1 AE related to dexamethasone	429	410	0	
≥ 1 AE related to melphalan	0	0	441	
≥ 1 AE related to prednisone	0	0	326	
≥ 1 AE related to thalidomide	0	0	493	

≥1 AE related to Len/Dex or MPT	269	269	145
≥ 1 Gr 3 or 4 AE related to Len/Dex/MPT	373	326	423
≥ 1 grade 3 or 4 AE related to Lenalidomide	342	290	0
≥ 1 grade 3 or 4 AE related to dexamethasone	229	177	0
≥ 1 grade 3 or 4 AE related to melphalan	0	0	307
≥ 1 grade 3 or 4 AE related to prednisone	0	0	118
≥ 1 grade 3 or 4 AE related to Thalidomide	0	0	316
≥1 Gr 3 or 4 AE related to Len/Dex or MPT	131	104	49
≥ 1 Grade 5 AE related to Len/Dex/MPT	17	11	10
≥ 1 Grade 5 AE related to Lenalidomide	12	9	0
≥ 1 Grade 5 AE related to Dexamethasone	16	7	0
≥ 1 Grade 5 AE related to melphalan	0	0	6
≥ 1 Grade 5 AE related to prednisone	0	0	5
≥ 1 Grade 5 AE related to Thalidomide	0	0	5
≥ 1 Grade 5 AE related to Len/Dex or MPT	11	5	2
≥1 SAE related to Len/Dex/MPT	195	158	142
≥1 SAE related to Lenalidomide	165	130	0
≥1 SAE related to dexamethasone	130	97	0
≥1 SAE related to melphalan	0	0	75
≥1 SAE related to prednisone	0	0	62
≥1 SAE related to thalidomide	0	0	94
≥1 SAE related to Len/Dex or MPT	95	64	27
≥1 AE leading to Len/Dex/MPT Withdrawal	157	109	153
≥1 AE leading to Lenalidomide withdrawal	109	93	0
≥1 AE leading to dexamethasone withdrawal	152	104	0
≥1 AE leading to melphalan withdrawal	0	0	83
≥1 AE leading to prednisone withdrawal	0	0	78
≥1 AE leading to Thalidomide withdrawal	0	0	146
≥1AE leading to Len/Dex OR MPT Withdrawal	96	84	71
≥1 AE leading to Len/Dex/MPT reduction	279	214	348
≥1 AE leading to Lenalidomide reduction	203	155	0
≥1 AE leading to dexamethasone reduction	170	118	0
≥1 AE leading to melphalan reduction	0	0	199
≥1 AE leading to prednisone reduction	0	0	47
≥1 AE leading to thalidomide reduction	0	0	254
≥1AE leading to Len/Dex OR MPT reduction	30	20	2
≥1 AE leading to Len/Dex/ MPT interruption	368	321	419
≥1 AE leading to Lenalidomide interruption	353	301	0

≥1 AE leading to dexamethasone interruption	319	280	0	
≥1 AE leading to melphalan interruption	0	0	328	
≥1 AE leading to prednisone interruption	0	0	324	
≥1 AE leading to Thalidomide interruption	0	0	388	
≥1 AE leading to Len/Dex or MPT interruption	290	241	249	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Shift from baseline to most extreme postbaseline value in creatinine clearance (CrCl) during the active treatment phase

End point title	Shift from baseline to most extreme postbaseline value in creatinine clearance (CrCl) during the active treatment phase
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End point description:

Renal function was assessed for participants from baseline to the most extreme value in creatinine clearance calculated using the Cockcroft-Gault estimation. Safety Population with baseline and postbaseline CrCl data.

End point type	Secondary
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End point timeframe:

Randomization to end of treatment or the data cut off of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	494	506	484	
Units: participants				
CrCl < 30 mL/min to CrCl < 30 mL/min	15	17	19	
CrCl < 30 mL/min to CrCl ≥ 30 but < 50 mL/min	18	14	19	
CrCl < 30 mL/min to CrCl ≥ 50 but < 80 mL/min	7	8	5	
CrCl < 30 mL/min to ≥ 80 mL/min	2	2	0	
CrCl ≥ 30 but < 50 mL/min to < 30 mL/min	1	2	0	
CrCl ≥ 30 but < 50 mL/min to CrCl ≥ 30 but < 50 mL	37	41	41	
CrCl ≥ 30 but < 50 mL/min to CrCl ≥ 50 but < 80 mL	67	55	65	
CrCl ≥ 30 but < 50 mL/min to ≥ 80 mL/min	9	12	2	
CrCl ≥ 50 but < 80 mL to CrCl < 30 mL/min	0	0	0	



CrCl $\geq$ 50 but < 80 mL to CrCl $\geq$ 30 but < 50 mL/min	4	1	4	
CrCl $\geq$ 50 but < 80 mL to CrCl $\geq$ 50 but < 80 mL/min	112	130	102	
CrCl $\geq$ 50 but < 80 mL to $\geq$ 80 mL/min	107	99	97	
CrCl $\geq$ 80 mL/min to CrCl < 30 mL/min	0	1	0	
CrCl $\geq$ 80 mL/min to CrCl $\geq$ 30 but < 50 mL/min	0	0	0	
CrCl $\geq$ 80 mL/min to CrCl $\geq$ 50 but < 80 mL/min	6	10	9	
CrCl $\geq$ 80 mL/min to CrCl $\geq$ 80 mL/min	109	114	121	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Shift from baseline to most extreme postbaseline value in absolute neutrophil count during the active treatment phase

End point title	Shift from baseline to most extreme postbaseline value in absolute neutrophil count during the active treatment phase
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End point description:

Neutrophil counts was assessed for participants from baseline grade to most extreme severity grade using the NCI CTCAE v 3.0 grading scale. Safety Population; includes participants with baseline and postbaseline absolute neutrophil laboratory test grade information.

End point type	Secondary
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End point timeframe:

Randomization to end of treatment or the data cut off of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	525	534	526	
Units: participants				
Normal Baseline Grade to Normal Postbaseline Grade	103	133	37	
Normal Baseline Grade to Grade 1 postbaseline	96	85	79	
Normal Baseline Grade to Grade 2 postbaseline	121	109	128	
Normal Baseline Grade to Grade 3 postbaseline	70	71	141	
Normal Baseline Grade to Grade 4 postbaseline	21	30	45	
Grade 1 Baseline to Normal postbaseline Grade	7	6	2	
Grade 1 Baseline to Grade 1 postbaseline	8	11	2	
Grade 1 Baseline to Grade 2 postbaseline	17	15	11	

Grade1 Baseline Grade to Grade3 postbaseline Grade	25	30	20	
Grade 1 Baseline to Grade 4 postbaseline	9	4	21	
Grade 2 Baseline to normal postbaseline Grade	1	0	0	
Grade 2 Baseline to Grade 1 postbaseline	1	1	1	
Grade 2 Baseline to Grade 2 postbaseline	14	11	7	
Grade 2 Baseline to Grade 3 postbaseline	18	18	21	
Grade 2 Baseline to Grade 4 postbaseline	9	5	10	
Grade 3 Baseline to Normal postbaseline Grade	0	0	0	
Grade 3 Baseline to Grade 1 postbaseline	0	0	0	
Grade 3 Baseline to Grade 2 postbaseline	2	1	0	
Grade 3 Baseline to Grade 3 postbaseline	2	2	0	
Grade 3 Baseline to Grade 4 postbaseline	0	2	1	
Grade 4 Baseline to Normal postbaseline Grade	0	0	0	
Grade 4 Baseline to Grade1 postbaseline Grade 1	1	0	0	
Grade 4 Baseline to Grade 2 postbaseline	0	0	0	
Grade 4 Baseline to Grade 3 postbaseline	0	0	0	
Grade 4 Baseline Grade to Grade 4 postbaseline	0	0	0	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Shift from baseline to most extreme in hemoglobin during the active treatment phase

End point title	Shift from baseline to most extreme in hemoglobin during the active treatment phase
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End point description:

Hemoglobin was assessed for participants from baseline grade to most extreme severity grade using the NCI CTCAE v 3.0 grading scale. Safety Population; Includes participants with baseline and postbaseline hemoglobin laboratory test grade information.

End point type	Secondary
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End point timeframe:

Randomization to end of treatment or the data cut off of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	527	535	526	
Units: participants				
Normal Baseline Grade to Normal Postbaseline Grade	6	10	9	
Normal Baseline Grade to Grade 1 postbaseline	39	30	25	
Normal Baseline Grade to Grade 2 postbaseline	8	8	4	
Normal Baseline Grade to Grade 3 postbaseline	0	1	1	
Normal Baseline Grade to Grade 4 postbaseline	0	0	0	
Grade 1 Baseline to Normal postbaseline Grade	0	0	0	
Grade 1 Baseline to Grade 1 postbaseline	106	126	110	
Grade 1 Baseline to Grade 2 postbaseline	128	123	123	
Grade 1 Baseline to Grade 3 postbaseline	25	17	20	
Grade 1 Baseline to Grade 4 postbaseline	2	5	4	
Grade 2 Baseline to normal postbaseline Grade	0	0	0	
Grade 2 Baseline to Grade 1 postbaseline	8	12	14	
Grade 2 Baseline to Grade 2 postbaseline	125	135	133	
Grade 2 Baseline to Grade 3 postbaseline	48	41	47	
Grade 2 Baseline to Grade 4 postbaseline	4	9	11	
Grade 3 Baseline to Normal postbaseline Grade	0	0	0	
Grade 3 Baseline to Grade 1 postbaseline	0	1	0	
Grade 3 Baseline to Grade 2 postbaseline	12	4	10	
Grade 3 Baseline to Grade 3 postbaseline	10	8	10	
Grade 3 Baseline to Grade 4 postbaseline	5	3	2	
Grade 4 Baseline to Normal postbaseline Grade	0	0	0	
Grade 4 Baseline to Grade 1 postbaseline	0	0	0	
Grade 4 Baseline to Grade 2 postbaseline	0	0	1	
Grade 4 Baseline to Grade 3 postbaseline	0	1	0	
Grade 4 Baseline to Grade 4 postbaseline	1	1	2	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Shift from baseline to most extreme postbaseline extreme value in platelet count during the active treatment phase

End point title	Shift from baseline to most extreme postbaseline extreme value in platelet count during the active treatment phase
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End point description:

Improvement in platelets was assessed for participants from baseline grade to most extreme severity grade using the NCI CTCAE v 3.0 grading scale. Safety population; includes participants with baseline and postbaseline platelet laboratory test grade information.

End point type	Secondary
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End point timeframe:

Randomization to end of treatment or the data cut off of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	527	535	526	
Units: participants				
Normal Baseline Grade to Normal Postbaseline Grade	197	197	165	
Normal Baseline Grade to Grade 1 postbaseline	216	211	208	
Normal Baseline Grade to Grade 2 postbaseline	24	30	27	
Normal Baseline Grade to Grade 3 postbaseline	15	12	31	
Normal Baseline Grade to Grade 4 postbaseline	4	5	11	
Grade 1 Baseline to Normal postbaseline Grade	1	3	6	
Grade 1 Baseline to Grade 1 postbaseline	34	38	51	
Grade 1 Baseline to Grade 2 postbaseline	15	19	7	
Grade 1 Baseline to Grade 3 postbaseline	10	12	10	
Grade 1 Baseline to Grade 4 postbaseline	2	1	1	
Grade 2 Baseline to normal postbaseline Grade	0	0	0	
Grade 2 Baseline to Grade 1 postbaseline	0	1	2	
Grade 2 Baseline to Grade 2 postbaseline	3	3	1	
Grade 2 Baseline to Grade 3 postbaseline	3	2	2	
Grade 2 Baseline to Grade 4 postbaseline	1	0	2	
Grade 3 Baseline to Normal postbaseline Grade	0	0	0	

Grade 3 Baseline to Grade 1 postbaseline	0	0	0	
Grade 3 Baseline to Grade 2 postbaseline	0	0	1	
Grade 3 Baseline to Grade 3 postbaseline	0	0	1	
Grade 3 Baseline to Grade 4 postbaseline	2	1	0	
Grade 4 Baseline to Normal postbaseline Grade	0	0	0	
Grade 4 Baseline to Grade 1 postbaseline	0	0	0	
Grade 4 Baseline to Grade 2 postbaseline	0	0	0	
Grade 4 Baseline to Grade 3 postbaseline	0	0	0	
Grade 4 Baseline to Grade 4 postbaseline	0	0	0	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Improvement of infection rate by observing the historical data compared to the clinical data base

End point title	Improvement of infection rate by observing the historical data compared to the clinical data base
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End point description:

Improvement of infection rate by observing historical data compared to the data within the clinical database was not analyzed.

End point type	Secondary
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End point timeframe:

Randomization to end of treatment or the data cut off of 24 May 2013; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[93]</sup>	0 <sup>[94]</sup>	0 <sup>[95]</sup>	
Units: participants				
number (not applicable)				

Notes:

[93] - Data for infection rate was not analyzed.

[94] - Data for infection rate was not analyzed.

[95] - Data for infection rate was not analyzed.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with an objective response after second-line anti-myeloma treatment at the Time of Final Analysis

End point title	Percentage of participants with an objective response after second-line anti-myeloma treatment at the Time of Final Analysis
End point description: Objective response according to IMWG Uniform Response Criteria was defined as a best overall response including a complete response (CR), very good partial response (VGPR) or partial response (PR) based on the Investigators Review. A CR is defined as: negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in BM; A VGPR is serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein and urine M-protein level $< 100$ mg/24 hours; A PR is: $\geq 50\%$ reduction of serum M-Protein and reduction in urinary M-protein by $\geq 90\%$ or to $< 200$ mg/24 hours. If present at baseline a $\geq 50\%$ reduction in size of soft tissue plasmacytomas. Includes ITT population that received second-line AMT.	
End point type	Secondary
End point timeframe: Disease response was assessed every 28 days until end of treatment or the data cut-off date of 21 January 2016; median duration of treatment was 80.2 weeks in the Rd arm; 72 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.	

End point values	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone Rd18	Melphalan + Prednisone + Thalidomide (MPT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	299	377	381	
Units: percentage of participants				
number (not applicable)	46.2	53.1	45.7	

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	680
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93824
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.38

Statistical analysis title	Statistical analysis 2
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Comparison groups	Lenalidomide and Low-Dose Dexamethasone (Rd) v Lenalidomide and Dexamethasone Rd18
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08836
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.03

<b>Statistical analysis title</b>	Statistical Analysis 3
Comparison groups	Lenalidomide and Dexamethasone Rd18 v Melphalan + Prednisone + Thalidomide (MPT)
Number of subjects included in analysis	758
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04974
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.79

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug treatment to at least 28 days after discontinuation of active treatment for those not continuing in the PFS phase; Up to the last study visit of 14 July 2016.

Adverse event reporting additional description:

Median duration of treatment was 80.2 weeks in the Rd arm, 72.0 weeks in the Rd18 arm and 67.1 weeks in the MPT arm.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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### Reporting groups

Reporting group title	Lenalidomide and Low-Dose Dexamethasone (Rd)
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Reporting group description:

Subjects received 25 mg lenalidomide (R) PO QD on days 1 to 21 of each 28-day treatment cycle plus 40 mg dexamethasone (d) PO QD on days 1, 8, 15, and 22 of a 28-day cycle until disease progression; (subjects > 75 years of age received 20 mg dexamethasone).

Reporting group title	Lenalidomide and Dexamethasone (Rd18)
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Reporting group description:

Subjects received 25 mg lenalidomide (R) PO on days 1 to 21 of each 28-day treatment cycle plus 40 mg dexamethasone (d) PO daily on days 1, 8, 15, and 22 of a 28-day cycle for 18 four-week cycle or until disease progression; (participants > 75 years of age received 20 mg dexamethasone).

Reporting group title	Melphalan + Prednisone + Thalidomide (MPT)
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Reporting group description:

Subjects received melphalan (M) 0.25 mg/kg PO QD on days 1 to 4 of each 42-day cycle up to 12 cycles plus prednisone (P) at 2 mg/kg PO QD on days 1 to 4 of each 42-day cycle up to 12 cycles and thalidomide (T) 200 mg PO QD on days 1 to 41 of each 42-day cycle for up to 12 cycles until progressive PD.

Serious adverse events	Lenalidomide and Low-Dose Dexamethasone (Rd)	Lenalidomide and Dexamethasone (Rd18)	Melphalan + Prednisone + Thalidomide (MPT)
Total subjects affected by serious adverse events			
subjects affected / exposed	378 / 532 (71.05%)	308 / 540 (57.04%)	270 / 541 (49.91%)
number of deaths (all causes)	55	36	38
number of deaths resulting from adverse events	17	11	10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ACUTE LYMPHOCYTIC LEUKAEMIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ACUTE MYELOID LEUKAEMIA			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BASAL CELL CARCINOMA</b>			
subjects affected / exposed	11 / 532 (2.07%)	4 / 540 (0.74%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	8 / 24	2 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BLADDER CANCER</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BLADDER TRANSITIONAL CELL CARCINOMA</b>			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BOWEN'S DISEASE</b>			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 6	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BREAST CANCER</b>			
subjects affected / exposed	1 / 532 (0.19%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>BREAST CANCER IN SITU</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CANCER PAIN</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>CARCINOID TUMOUR OF THE APPENDIX</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC MYXOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
COLON ADENOMA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
COLON CANCER METASTATIC			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
COLON CANCER STAGE IV			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ENDOMETRIAL CANCER METASTATIC			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
ENDOMETRIAL CANCER STAGE III			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
GASTRIC CANCER			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
GASTROINTESTINAL NEOPLASM			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HEPATIC NEOPLASM MALIGNANT			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
LENTIGO MALIGNA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEUKAEMIA PLASMACYTIC			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ADENOCARCINOMA METASTATIC			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
LUNG ADENOCARCINOMA STAGE IV			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
LUNG CANCER METASTATIC			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG NEOPLASM			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
LUNG NEOPLASM MALIGNANT			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG SQUAMOUS CELL CARCINOMA STAGE I			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
LUNG SQUAMOUS CELL CARCINOMA STAGE UNSPECIFIED			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
MENINGIOMA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METASTASES TO CENTRAL NERVOUS SYSTEM			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
METASTATIC MALIGNANT MELANOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
MULTIPLE MYELOMA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEOPLASM SWELLING			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OESOPHAGEAL ADENOCARCINOMA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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 NEOPLASM BENIGN			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PLASMACYTOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PROSTATE CANCER			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (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
PROSTATE CANCER RECURRENT			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PROSTATIC ADENOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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			

subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
SALIVARY GLAND CANCER			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SMALL INTESTINE CARCINOMA METASTATIC			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	16 / 532 (3.01%)	5 / 540 (0.93%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	20 / 37	2 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSITIONAL CELL CANCER OF THE RENAL PELVIS AND URETER			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
TUMOUR FLARE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
AORTIC ANEURYSM			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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

AORTIC ANEURYSM RUPTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
AORTIC DISSECTION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ARTERIAL HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEEP VEIN THROMBOSIS			
subjects affected / exposed	19 / 532 (3.57%)	11 / 540 (2.04%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	18 / 19	10 / 11	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMATOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HYPERTENSION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSIVE CRISIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	8 / 532 (1.50%)	7 / 540 (1.30%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 9	1 / 9	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOVOLAEMIC SHOCK			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORTHOSTATIC HYPOTENSION			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PERIPHERAL ARTERY ANEURYSM			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PERIPHERAL ARTERY THROMBOSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHLEBITIS			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	5 / 541 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SHOCK			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
THROMBOPHLEBITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
THROMBOPHLEBITIS SUPERFICIAL			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
THROMBOSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENOUS THROMBOSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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	12 / 532 (2.26%)	2 / 540 (0.37%)	5 / 541 (0.92%)
occurrences causally related to treatment / all	2 / 16	2 / 3	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST DISCOMFORT			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 PAIN			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CHILLS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
DEATH			
subjects affected / exposed	3 / 532 (0.56%)	3 / 540 (0.56%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 3	1 / 3	1 / 1
deaths causally related to treatment / all	1 / 3	1 / 3	1 / 1
FATIGUE			

subjects affected / exposed	3 / 532 (0.56%)	3 / 540 (0.56%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	2 / 3	2 / 4	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	16 / 532 (3.01%)	13 / 540 (2.41%)	12 / 541 (2.22%)
occurrences causally related to treatment / all	7 / 17	4 / 17	5 / 16
deaths causally related to treatment / all	1 / 2	0 / 4	1 / 6
GENERALISED OEDEMA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
HYPERPYREXIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HYPERTHERMIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HYPOTHERMIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLAMMATION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
INJECTION SITE HAEMORRHAGE			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>MALAISE</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>MUCOSAL INFLAMMATION</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>MULTI-ORGAN FAILURE</b>			
subjects affected / exposed	0 / 532 (0.00%)	3 / 540 (0.56%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 3	1 / 3
<b>NON-CARDIAC CHEST PAIN</b>			
subjects affected / exposed	4 / 532 (0.75%)	4 / 540 (0.74%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>OEDEMA PERIPHERAL</b>			
subjects affected / exposed	5 / 532 (0.94%)	2 / 540 (0.37%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	1 / 5	3 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PAIN</b>			
subjects affected / exposed	5 / 532 (0.94%)	0 / 540 (0.00%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PERFORMANCE STATUS DECREASED</b>			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PYREXIA</b>			

subjects affected / exposed	22 / 532 (4.14%)	11 / 540 (2.04%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	3 / 29	5 / 15	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL PAIN			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN DEATH			
subjects affected / exposed	5 / 532 (0.94%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	1 / 5	0 / 2	0 / 2
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
AMYLOIDOSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ANAPHYLACTIC SHOCK			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HYPERSENSITIVITY			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
EPIDIDYMITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
GENITAL PROLAPSE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PROSTATITIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
Respiratory, thoracic and mediastinal disorders			
ACUTE PULMONARY OEDEMA			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
ACUTE RESPIRATORY FAILURE			

subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 3	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 1	1 / 1	1 / 1
ASTHMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
BRONCHIECTASIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMOPATHY			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	12 / 532 (2.26%)	5 / 540 (0.93%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	2 / 16	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COUGH			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSпноEA			
subjects affected / exposed	14 / 532 (2.63%)	7 / 540 (1.30%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	2 / 15	5 / 8	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSпноEA EXERTIONAL			

subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPISTAXIS			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 2	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOPTYSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HAEMOTHORAX			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HYPOXIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG DISORDER			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PLEURAL EFFUSION			
subjects affected / exposed	1 / 532 (0.19%)	3 / 540 (0.56%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PNEUMONIA ASPIRATION			

subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY ALVEOLAR HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY ARTERIAL HYPERTENSION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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	20 / 532 (3.76%)	15 / 540 (2.78%)	20 / 541 (3.70%)
occurrences causally related to treatment / all	21 / 21	15 / 15	18 / 21
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
PULMONARY HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
PULMONARY HYPERTENSION			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY INFARCTION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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 OEDEMA			
subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 7	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY THROMBOSIS			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
RESPIRATORY ALKALOSIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY DISTRESS			
subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 4	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	8 / 532 (1.50%)	5 / 540 (0.93%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	1 / 8	4 / 6	1 / 4
deaths causally related to treatment / all	0 / 1	3 / 3	0 / 0
SLEEP APNOEA SYNDROME			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
AGITATED DEPRESSION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
ANXIETY			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COMPLETED SUICIDE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
CONFUSIONAL STATE			

subjects affected / exposed	7 / 532 (1.32%)	6 / 540 (1.11%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	4 / 8	3 / 7	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
<b>DELIRIUM</b>			
subjects affected / exposed	4 / 532 (0.75%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 4	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>DEPRESSED MOOD</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>DEPRESSION</b>			
subjects affected / exposed	4 / 532 (0.75%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>DISORIENTATION</b>			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>EUPHORIC MOOD</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>HALLUCINATION</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>IMPAIRED SELF-CARE</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>MAJOR DEPRESSION</b>			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>MENTAL STATUS CHANGES</b>			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>SUICIDE ATTEMPT</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>Investigations</b>			
<b>ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>ALANINE AMINOTRANSFERASE INCREASED</b>			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
<b>ASPARTATE AMINOTRANSFERASE INCREASED</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>BIOPSY BONE MARROW ABNORMAL</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>BLOOD BILIRUBIN INCREASED</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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

BLOOD CREATININE INCREASED			
subjects affected / exposed	2 / 532 (0.38%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS WORSENER			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
EJECTION FRACTION DECREASED			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMOGLOBIN ABNORMAL			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HEART RATE INCREASED			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HEPATIC ENZYME INCREASED			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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

LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PROTEIN URINE PRESENT			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PROTHROMBIN TIME RATIO INCREASED			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
TROPONIN INCREASED			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
TROPONIN T INCREASED			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
WEIGHT DECREASED			
subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
ACCIDENTAL OVERDOSE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 1	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACETABULUM FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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

ALCOHOL POISONING			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ANKLE FRACTURE			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (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
BLADDER INJURY			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLAVICLE FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
CONTUSION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
CRANIOCEREBRAL INJURY			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FACE INJURY			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			

subjects affected / exposed	5 / 532 (0.94%)	3 / 540 (0.56%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	1 / 5	1 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMORAL NECK FRACTURE			
subjects affected / exposed	3 / 532 (0.56%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			
subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FOOT FRACTURE			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (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
FRACTURED SACRUM			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HEAD INJURY			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HEART INJURY			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIP FRACTURE			
subjects affected / exposed	4 / 532 (0.75%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			

subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INCISIONAL HERNIA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
INFUSION RELATED REACTION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
JAW FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
JOINT DISLOCATION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
LACERATION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MEDICATION ERROR			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENISCUS LESION			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OVERDOSE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PUBIS FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RADIUS FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 FUME INHALATION DISORDER			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
RIB FRACTURE			
subjects affected / exposed	2 / 532 (0.38%)	3 / 540 (0.56%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL COMPRESSION FRACTURE			

subjects affected / exposed	6 / 532 (1.13%)	3 / 540 (0.56%)	5 / 541 (0.92%)
occurrences causally related to treatment / all	3 / 7	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STERNAL FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
TENDON RUPTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (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
TRANSFUSION-RELATED ACUTE LUNG INJURY			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
TRAUMATIC FRACTURE			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ULNA FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER LIMB FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
WRIST FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
LEFT VENTRICLE OUTFLOW TRACT OBSTRUCTION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THALASSAEMIA BETA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	5 / 532 (0.94%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	2 / 6	2 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

ANGINA PECTORIS			
subjects affected / exposed	7 / 532 (1.32%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 7	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARRHYTHMIA			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARRHYTHMIA SUPRAVENTRICULAR			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
ARTERIOSCLEROSIS CORONARY ARTERY			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION			
subjects affected / exposed	18 / 532 (3.38%)	12 / 540 (2.22%)	9 / 541 (1.66%)
occurrences causally related to treatment / all	8 / 22	3 / 13	2 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	3 / 532 (0.56%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 3	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL THROMBOSIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYARRHYTHMIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRADYCARDIA			
subjects affected / exposed	2 / 532 (0.38%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 2	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC AMYLOIDOSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
subjects affected / exposed	5 / 532 (0.94%)	3 / 540 (0.56%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	13 / 532 (2.44%)	11 / 540 (2.04%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	3 / 22	5 / 17	5 / 9
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 1
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	7 / 532 (1.32%)	5 / 540 (0.93%)	5 / 541 (0.92%)
occurrences causally related to treatment / all	0 / 11	3 / 8	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FLUTTER			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
CARDIOGENIC SHOCK			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
CARDIOMYOPATHY			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
CARDIOPULMONARY FAILURE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
CONGESTIVE CARDIOMYOPATHY			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
COR PULMONALE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
CORONARY ARTERY DISEASE			
subjects affected / exposed	5 / 532 (0.94%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY INSUFFICIENCY			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY STENOSIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIASTOLIC DYSFUNCTION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HYPERTENSIVE HEART DISEASE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
LEFT VENTRICULAR DYSFUNCTION			
subjects affected / exposed	1 / 532 (0.19%)	2 / 540 (0.37%)	0 / 541 (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
LEFT VENTRICULAR FAILURE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDIAL INFARCTION			
subjects affected / exposed	7 / 532 (1.32%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 8	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 2	1 / 1	1 / 1
MYOCARDIAL ISCHAEMIA			

subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
NODAL ARRHYTHMIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PALPITATIONS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PERICARDITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SICK SINUS SYNDROME			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SINOATRIAL BLOCK			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS ARREST			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SINUS BRADYCARDIA			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 532 (0.19%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TACHYARRHYTHMIA			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
TACHYCARDIA			
subjects affected / exposed	1 / 532 (0.19%)	4 / 540 (0.74%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VENTRICULAR FLUTTER			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
VENTRICULAR TACHYCARDIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
APHASIA			

subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (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
<b>BRAIN STEM INFARCTION</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
<b>CAROTID ARTERY STENOSIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>CAUDA EQUINA SYNDROME</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>CEREBRAL HAEMORRHAGE</b>			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
<b>CEREBRAL INFARCTION</b>			
subjects affected / exposed	4 / 532 (0.75%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 4	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CEREBRAL ISCHAEMIA</b>			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CEREBROVASCULAR ACCIDENT</b>			
subjects affected / exposed	8 / 532 (1.50%)	3 / 540 (0.56%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	3 / 9	3 / 3	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
<b>COMA</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
CONVULSION			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COORDINATION ABNORMAL			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEMENTIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
DIZZINESS			
subjects affected / exposed	5 / 532 (0.94%)	0 / 540 (0.00%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	0 / 6	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSTONIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPIDURITIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
EPILEPSY			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GRAND MAL CONVULSION			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
GUILLAIN-BARRE SYNDROME			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HEADACHE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HYPOAESTHESIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ISCHAEMIC CEREBRAL INFARCTION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ISCHAEMIC STROKE			
subjects affected / exposed	4 / 532 (0.75%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LACUNAR INFARCTION			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
LETHARGY			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	1 / 532 (0.19%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MOTOR NEURONE DISEASE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAESTHESIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARALYSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARAPARESIS			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (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
PARAPLEGIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PARKINSON'S DISEASE			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PARKINSONISM</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>PERIPHERAL MOTOR NEUROPATHY</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PERIPHERAL SENSORIMOTOR NEUROPATHY</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PERIPHERAL SENSORY NEUROPATHY</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>POLYNEUROPATHY</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>POST HERPETIC NEURALGIA</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>PRESYNCOPE</b>			
subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 6	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PYRAMIDAL TRACT SYNDROME</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
RADICULITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
REPETITIVE SPEECH			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SCIATICA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SOMNOLENCE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SPEECH DISORDER			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 CORD COMPRESSION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBARACHNOID HAEMORRHAGE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SYNCOPE			

subjects affected / exposed	9 / 532 (1.69%)	3 / 540 (0.56%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	2 / 10	1 / 3	5 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT GLOBAL AMNESIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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	2 / 532 (0.38%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 2	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRIGEMINAL NEURALGIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VASCULAR ENCEPHALOPATHY			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	24 / 532 (4.51%)	15 / 540 (2.78%)	23 / 541 (4.25%)
occurrences causally related to treatment / all	9 / 31	12 / 19	17 / 29
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA HAEMOLYTIC AUTOIMMUNE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
FEBRILE BONE MARROW APLASIA			



subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>FEBRILE NEUTROPENIA</b>			
subjects affected / exposed	5 / 532 (0.94%)	8 / 540 (1.48%)	13 / 541 (2.40%)
occurrences causally related to treatment / all	4 / 5	8 / 8	12 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>HAEMOLYSIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>HYPERVISCOSITY SYNDROME</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>HYPOCOAGULABLE STATE</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>IDIOPATHIC THROMBOCYTOPENIC PURPURA</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>LEUKOPENIA</b>			
subjects affected / exposed	0 / 532 (0.00%)	3 / 540 (0.56%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	0 / 0	4 / 5	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>LYMPHADENITIS</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>LYMPHOPENIA</b>			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>NEUTROPENIA</b>			
subjects affected / exposed	9 / 532 (1.69%)	5 / 540 (0.93%)	7 / 541 (1.29%)
occurrences causally related to treatment / all	9 / 10	4 / 5	7 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>PANCYTOPENIA</b>			
subjects affected / exposed	1 / 532 (0.19%)	2 / 540 (0.37%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	0 / 1	2 / 2	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>THROMBOCYTOPENIA</b>			
subjects affected / exposed	5 / 532 (0.94%)	6 / 540 (1.11%)	10 / 541 (1.85%)
occurrences causally related to treatment / all	2 / 5	10 / 12	8 / 13
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Ear and labyrinth disorders</b>			
<b>VERTIGO</b>			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Eye disorders</b>			
<b>BLINDNESS UNILATERAL</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>CATARACT</b>			
subjects affected / exposed	5 / 532 (0.94%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 8	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>CHOROIDAL DETACHMENT</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>CONJUNCTIVAL OEDEMA</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
DIPLOPIA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
GLAUCOMA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
OCULAR HYPERTENSION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
UVEITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
VISION BLURRED			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ABDOMINAL PAIN			

subjects affected / exposed	5 / 532 (0.94%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 5	0 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 532 (0.00%)	3 / 540 (0.56%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL WALL HAEMATOMA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
COLITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
COLITIS ISCHAEMIC			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
COLONIC POLYP			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	5 / 532 (0.94%)	3 / 540 (0.56%)	5 / 541 (0.92%)
occurrences causally related to treatment / all	4 / 5	1 / 3	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	9 / 532 (1.69%)	8 / 540 (1.48%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	5 / 9	4 / 8	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULAR PERFORATION			

subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
<b>DIVERTICULUM</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>DYSPHAGIA</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ENTERITIS</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>ENTEROCOLITIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>ENTEROCUTANEOUS FISTULA</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ENTEROVESICAL FISTULA</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>FAECALOMA</b>			
subjects affected / exposed	0 / 532 (0.00%)	3 / 540 (0.56%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>GASTRIC DISORDER</b>			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>GASTRIC ULCER</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>GASTRIC ULCER HAEMORRHAGE</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>GASTRITIS</b>			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	0 / 541 (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
<b>GASTROINTESTINAL HAEMORRHAGE</b>			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>GASTROINTESTINAL MOTILITY DISORDER</b>			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
<b>GASTROINTESTINAL NECROSIS</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>GASTROINTESTINAL STENOSIS</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>GINGIVAL BLEEDING</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HAEMATEMESIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HAEMORRHAGIC EROSIVE GASTRITIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIATUS HERNIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ILEUS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEUS PARALYTIC			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
INGUINAL HERNIA			
subjects affected / exposed	3 / 532 (0.56%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INGUINAL HERNIA STRANGULATED			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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, OBSTRUCTIVE			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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 ISCHAEMIA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	4 / 532 (0.75%)	3 / 540 (0.56%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 4	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
LARGE INTESTINE PERFORATION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
NAUSEA			
subjects affected / exposed	6 / 532 (1.13%)	2 / 540 (0.37%)	7 / 541 (1.29%)
occurrences causally related to treatment / all	2 / 6	0 / 2	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NECROTISING COLITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OBSTRUCTION GASTRIC			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OESOPHAGEAL STENOSIS			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OESOPHAGITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ORAL DISORDER			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PANCREATITIS			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PEPTIC ULCER HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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 PERFORATION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
REFLUX GASTRITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SIGMOIDITIS			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBILEUS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
TONGUE HAEMATOMA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
UMBILICAL HERNIA, OBSTRUCTIVE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	8 / 532 (1.50%)	4 / 540 (0.74%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	2 / 8	0 / 6	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILE DUCT OBSTRUCTION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
BILE DUCT STONE			

subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
CHOLANGITIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
CHOLECYSTITIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
CHOLELITHIASIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HEPATIC FAILURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HEPATITIS ACUTE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HYPERBILIRUBINAEMIA			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>HYPERTRANSAMINASAEMIA</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>LIVER DISORDER</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>Skin and subcutaneous tissue disorders</b>			
<b>ACTINIC KERATOSIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ACUTE FEBRILE NEUTROPHILIC DERMATOSIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>CUTANEOUS VASCULITIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>DECUBITUS ULCER</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>DERMATITIS ALLERGIC</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>DERMATITIS EXFOLIATIVE</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
DRUG ERUPTION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
EXFOLIATIVE RASH			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
HYPERHIDROSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PRURITUS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH			
subjects affected / exposed	5 / 532 (0.94%)	5 / 540 (0.93%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	5 / 6	3 / 5	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH ERYTHEMATOUS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 MACULAR			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
RASH MACULO-PAPULAR			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RASH PRURITIC			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
SKIN ULCER			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
TOXIC EPIDERMAL NECROLYSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
Renal and urinary disorders			
ACUTE PRERENAL FAILURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
AZOTAEMIA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLADDER PROLAPSE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
DYSURIA			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HAEMATURIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OLIGURIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PROTEINURIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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 ARTERY STENOSIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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 COLIC			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
RENAL FAILURE			
subjects affected / exposed	8 / 532 (1.50%)	18 / 540 (3.33%)	14 / 541 (2.59%)
occurrences causally related to treatment / all	1 / 8	4 / 25	3 / 23
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
RENAL FAILURE ACUTE			
subjects affected / exposed	21 / 532 (3.95%)	16 / 540 (2.96%)	10 / 541 (1.85%)
occurrences causally related to treatment / all	6 / 22	5 / 16	2 / 12
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
RENAL FAILURE CHRONIC			

subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
RENAL IMPAIRMENT			
subjects affected / exposed	5 / 532 (0.94%)	2 / 540 (0.37%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	1 / 5	1 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY BLADDER HAEMORRHAGE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY RETENTION			
subjects affected / exposed	2 / 532 (0.38%)	4 / 540 (0.74%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
HYPERTHYROIDISM			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
THYROID CYST			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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 / 532 (0.19%)	2 / 540 (0.37%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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



BACK PAIN			
subjects affected / exposed	22 / 532 (4.14%)	19 / 540 (3.52%)	10 / 541 (1.85%)
occurrences causally related to treatment / all	2 / 28	1 / 23	1 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BONE LESION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
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 PAIN			
subjects affected / exposed	10 / 532 (1.88%)	6 / 540 (1.11%)	6 / 541 (1.11%)
occurrences causally related to treatment / all	0 / 11	0 / 6	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CHONDROCALCINOSIS PYROPHOSPHATE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
DUPUYTREN'S CONTRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
FIBROMYALGIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
FLANK PAIN			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
GOUTY ARTHRITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
GOUTY TOPHUS			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 DEGENERATION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTERVERTEBRAL DISC DISORDER			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	0 / 541 (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
LUMBAR SPINAL STENOSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
MONARTHROSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
MYALGIA			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
MYOPATHY			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
NECK PAIN			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOARTHRITIS			
subjects affected / exposed	2 / 532 (0.38%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOCHONDROSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OSTEOLYSIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEONECROSIS			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OSTEONECROSIS OF JAW			
subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOPOROSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
OSTEOPOROTIC FRACTURE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PATHOLOGICAL FRACTURE			
subjects affected / exposed	0 / 532 (0.00%)	4 / 540 (0.74%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POLYARTHRITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
SOFT TISSUE MASS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 COLUMN STENOSIS			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>SPINAL DISORDER</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>SYNOVIAL CYST</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>VERTEBRAL WEDGING</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>Infections and infestations</b>			
<b>ABDOMINAL ABSCESS</b>			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>ABDOMINAL WALL ABSCESS</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>ABSCESS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>ABSCESS LIMB</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>ANORECTAL INFECTION BACTERIAL</b>			

subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
APPENDICITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS BACTERIAL			
subjects affected / exposed	5 / 532 (0.94%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS INFECTIVE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
ATYPICAL PNEUMONIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
BACTERAEemia			
subjects affected / exposed	3 / 532 (0.56%)	2 / 540 (0.37%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 3	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACTERIAL SEPSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
BRONCHITIS			
subjects affected / exposed	13 / 532 (2.44%)	6 / 540 (1.11%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	4 / 15	2 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			

subjects affected / exposed	2 / 532 (0.38%)	5 / 540 (0.93%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	1 / 2	5 / 6	1 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
BURSITIS INFECTIVE STAPHYLOCOCCAL			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
CAMPYLOBACTER INFECTION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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	8 / 532 (1.50%)	3 / 540 (0.56%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	5 / 13	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS INFECTIVE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIAL INFECTION			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
CYSTITIS			

subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 INFECTIOUS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
DIVERTICULITIS			
subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DOUGLAS' ABSCESS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
EMBOLIC PNEUMONIA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ENDOCARDITIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS BACTERIAL			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENDOCARDITIS STAPHYLOCOCCAL			



subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ENDOPHTHALMITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
ENTEROCOCCAL SEPSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
EPIGLOTTITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
ERYSIPELAS			
subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA SEPSIS			
subjects affected / exposed	0 / 532 (0.00%)	3 / 540 (0.56%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
FUNGAL INFECTION			

subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FURUNCLE			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
GASTROENTERITIS			
subjects affected / exposed	0 / 532 (0.00%)	3 / 540 (0.56%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS SALMONELLA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
GASTROENTERITIS VIRAL			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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 INFECTION			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
HEPATITIS B			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
HERPES ZOSTER			
subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTION			

subjects affected / exposed	4 / 532 (0.75%)	1 / 540 (0.19%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	4 / 532 (0.75%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIVE TENOSYNOVITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
INFLUENZA			
subjects affected / exposed	7 / 532 (1.32%)	3 / 540 (0.56%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 8	0 / 3	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
INTERVERTEBRAL DISCITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
KLEBSIELLA BACTERAEemia			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
KLEBSIELLA INFECTION			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KLEBSIELLA SEPSIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOBAR PNEUMONIA			

subjects affected / exposed	8 / 532 (1.50%)	7 / 540 (1.30%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	4 / 9	2 / 7	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
LOCALISED INFECTION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 532 (1.50%)	3 / 540 (0.56%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	3 / 15	1 / 3	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
subjects affected / exposed	3 / 532 (0.56%)	8 / 540 (1.48%)	5 / 541 (0.92%)
occurrences causally related to treatment / all	1 / 3	5 / 9	2 / 6
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
LUNG INFECTION PSEUDOMONAL			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
MENINGITIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
MENINGITIS CRYPTOCOCCAL			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
MENINGOCOCCAL SEPSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
NEUTROPENIC SEPSIS			

subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	1 / 1	1 / 1	1 / 1
OESOPHAGEAL CANDIDIASIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
ORCHITIS			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
OROPHARYNGEAL CANDIDIASIS			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PERIODONTITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PERIORBITAL ABSCESS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PERIORBITAL CELLULITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PERITONITIS			

subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
PNEUMOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PNEUMOCOCCAL SEPSIS			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECI PNEUMONIA			
subjects affected / exposed	3 / 532 (0.56%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
PNEUMONIA			
subjects affected / exposed	60 / 532 (11.28%)	48 / 540 (8.89%)	35 / 541 (6.47%)
occurrences causally related to treatment / all	37 / 71	28 / 59	17 / 42
deaths causally related to treatment / all	3 / 6	1 / 2	0 / 0
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ESCHERICHIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PNEUMONIA KLEBSIELLA			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PNEUMONIA LEGIONELLA			

subjects affected / exposed	2 / 532 (0.38%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	4 / 532 (0.75%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 4	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
PNEUMONIA STAPHYLOCOCCAL			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
PNEUMONIA STREPTOCOCCAL			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PNEUMONIA VIRAL			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POST PROCEDURAL SEPSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
POSTOPERATIVE ABSCESS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PROSTATIC ABSCESS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
PSEUDOMEMBRANOUS COLITIS			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PSEUDOMONAL SEPSIS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
PULMONARY TUBERCULOSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
PYELONEPHRITIS			
subjects affected / exposed	4 / 532 (0.75%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYELONEPHRITIS ACUTE			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	9 / 532 (1.69%)	5 / 540 (0.93%)	4 / 541 (0.74%)
occurrences causally related to treatment / all	3 / 11	3 / 5	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	17 / 532 (3.20%)	10 / 540 (1.85%)	8 / 541 (1.48%)
occurrences causally related to treatment / all	7 / 25	6 / 12	4 / 10
deaths causally related to treatment / all	3 / 7	1 / 3	2 / 4
SEPTIC SHOCK			



subjects affected / exposed	5 / 532 (0.94%)	7 / 540 (1.30%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	4 / 8	1 / 10	0 / 3
deaths causally related to treatment / all	2 / 4	0 / 5	0 / 3
<b>SINUSITIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>SOFT TISSUE INFECTION</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>STAPHYLOCOCCAL BACTERAEMIA</b>			
subjects affected / exposed	4 / 532 (0.75%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>STAPHYLOCOCCAL IMPETIGO</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>STAPHYLOCOCCAL INFECTION</b>			
subjects affected / exposed	1 / 532 (0.19%)	1 / 540 (0.19%)	0 / 541 (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
<b>STAPHYLOCOCCAL SEPSIS</b>			
subjects affected / exposed	2 / 532 (0.38%)	3 / 540 (0.56%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
<b>STRONGYLOIDIASIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>SUBCUTANEOUS ABSCESS</b>			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
TOOTH ABSCESS			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
TRACHEOBRONCHITIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
TUBERCULOSIS			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
TUBERCULOUS PLEURISY			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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	8 / 532 (1.50%)	9 / 540 (1.67%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	4 / 8	3 / 10	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	9 / 532 (1.69%)	5 / 540 (0.93%)	3 / 541 (0.55%)
occurrences causally related to treatment / all	2 / 12	1 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION BACTERIAL			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UROSEPSIS			

subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WHIPPLE'S DISEASE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
CACHEXIA			
subjects affected / exposed	2 / 532 (0.38%)	0 / 540 (0.00%)	0 / 541 (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
DECREASED APPETITE			
subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 7	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	7 / 532 (1.32%)	9 / 540 (1.67%)	7 / 541 (1.29%)
occurrences causally related to treatment / all	1 / 8	4 / 13	3 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS			
subjects affected / exposed	3 / 532 (0.56%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	3 / 3	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FAILURE TO THRIVE			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
FOOD INTOLERANCE			

subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GOUT			
subjects affected / exposed	3 / 532 (0.56%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERCALCAEMIA			
subjects affected / exposed	5 / 532 (0.94%)	10 / 540 (1.85%)	7 / 541 (1.29%)
occurrences causally related to treatment / all	0 / 6	0 / 10	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	4 / 532 (0.75%)	3 / 540 (0.56%)	0 / 541 (0.00%)
occurrences causally related to treatment / all	2 / 5	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIC HYPEROSMOLAR NONKETOTIC SYNDROME			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
HYPERKALAEMIA			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	2 / 541 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERURICAEMIA			
subjects affected / exposed	0 / 532 (0.00%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 532 (0.19%)	2 / 540 (0.37%)	0 / 541 (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
HYPOCALCAEMIA			

subjects affected / exposed	5 / 532 (0.94%)	4 / 540 (0.74%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	1 / 5	0 / 8	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>HYPOGLYCAEMIA</b>			
subjects affected / exposed	4 / 532 (0.75%)	2 / 540 (0.37%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>HYPOKALAEMIA</b>			
subjects affected / exposed	6 / 532 (1.13%)	1 / 540 (0.19%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 7	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>HYPOMAGNESAEMIA</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>HYPONATRAEMIA</b>			
subjects affected / exposed	6 / 532 (1.13%)	6 / 540 (1.11%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	2 / 7	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>HYPOPROTEINAEMIA</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>IRON DEFICIENCY</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>MALNUTRITION</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>MARASMUS</b>			

subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>METABOLIC ACIDOSIS</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	1 / 541 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>METABOLIC ALKALOSIS</b>			
subjects affected / exposed	0 / 532 (0.00%)	1 / 540 (0.19%)	0 / 541 (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
<b>SHOCK HYPOGLYCAEMIC</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>TETANY</b>			
subjects affected / exposed	1 / 532 (0.19%)	0 / 540 (0.00%)	0 / 541 (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
<b>TYPE 2 DIABETES MELLITUS</b>			
subjects affected / exposed	0 / 532 (0.00%)	2 / 540 (0.37%)	0 / 541 (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

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	<b>Lenalidomide and Low-Dose Dexamethasone (Rd)</b>	<b>Lenalidomide and Dexamethasone (Rd18)</b>	<b>Melphalan + Prednisone + Thalidomide (MPT)</b>
Total subjects affected by non-serious adverse events			
subjects affected / exposed	523 / 532 (98.31%)	532 / 540 (98.52%)	532 / 541 (98.34%)
<b>Vascular disorders</b>			
<b>DEEP VEIN THROMBOSIS</b>			
subjects affected / exposed	40 / 532 (7.52%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	44	0	0

HYPERTENSION			
subjects affected / exposed	43 / 532 (8.08%)	27 / 540 (5.00%)	35 / 541 (6.47%)
occurrences (all)	45	30	39
HYPOTENSION			
subjects affected / exposed	52 / 532 (9.77%)	28 / 540 (5.19%)	35 / 541 (6.47%)
occurrences (all)	59	30	38
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	148 / 532 (27.82%)	122 / 540 (22.59%)	123 / 541 (22.74%)
occurrences (all)	360	217	211
FATIGUE			
subjects affected / exposed	178 / 532 (33.46%)	176 / 540 (32.59%)	153 / 541 (28.28%)
occurrences (all)	411	358	287
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	31 / 532 (5.83%)	27 / 540 (5.00%)	0 / 541 (0.00%)
occurrences (all)	44	33	0
OEDEMA			
subjects affected / exposed	38 / 532 (7.14%)	28 / 540 (5.19%)	32 / 541 (5.91%)
occurrences (all)	64	33	40
OEDEMA PERIPHERAL			
subjects affected / exposed	220 / 532 (41.35%)	168 / 540 (31.11%)	213 / 541 (39.37%)
occurrences (all)	417	295	343
PYREXIA			
subjects affected / exposed	111 / 532 (20.86%)	94 / 540 (17.41%)	69 / 541 (12.75%)
occurrences (all)	165	159	96
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	129 / 532 (24.25%)	94 / 540 (17.41%)	67 / 541 (12.38%)
occurrences (all)	199	118	84
DYSPHONIA			
subjects affected / exposed	31 / 532 (5.83%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	35	0	0
DYSPNOEA			
subjects affected / exposed	112 / 532 (21.05%)	85 / 540 (15.74%)	110 / 541 (20.33%)
occurrences (all)	176	124	153
DYSPNOEA EXERTIONAL			

subjects affected / exposed	30 / 532 (5.64%)	28 / 540 (5.19%)	0 / 541 (0.00%)
occurrences (all)	42	32	0
EPISTAXIS			
subjects affected / exposed	32 / 532 (6.02%)	31 / 540 (5.74%)	0 / 541 (0.00%)
occurrences (all)	44	39	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	32 / 532 (6.02%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	36	0	0
PRODUCTIVE COUGH			
subjects affected / exposed	35 / 532 (6.58%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	52	0	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	45 / 532 (8.46%)	36 / 540 (6.67%)	41 / 541 (7.58%)
occurrences (all)	54	44	45
CONFUSIONAL STATE			
subjects affected / exposed	35 / 532 (6.58%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	40	0	0
DEPRESSION			
subjects affected / exposed	66 / 532 (12.41%)	45 / 540 (8.33%)	30 / 541 (5.55%)
occurrences (all)	81	54	36
INSOMNIA			
subjects affected / exposed	150 / 532 (28.20%)	127 / 540 (23.52%)	53 / 541 (9.80%)
occurrences (all)	219	196	58
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	39 / 532 (7.33%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	74	0	0
WEIGHT DECREASED			
subjects affected / exposed	73 / 532 (13.72%)	78 / 540 (14.44%)	47 / 541 (8.69%)
occurrences (all)	105	102	63
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	39 / 532 (7.33%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	56	0	0
FALL			



subjects affected / exposed occurrences (all)	46 / 532 (8.65%) 63	0 / 540 (0.00%) 0	0 / 541 (0.00%) 0
Cardiac disorders ATRIAL FIBRILLATION subjects affected / exposed occurrences (all)	30 / 532 (5.64%) 37	0 / 540 (0.00%) 0	0 / 541 (0.00%) 0
Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all)	87 / 532 (16.35%) 107	70 / 540 (12.96%) 91	114 / 541 (21.07%) 194
DYSGEUSIA subjects affected / exposed occurrences (all)	41 / 532 (7.71%) 56	45 / 540 (8.33%) 54	0 / 541 (0.00%) 0
HEADACHE subjects affected / exposed occurrences (all)	80 / 532 (15.04%) 120	52 / 540 (9.63%) 61	55 / 541 (10.17%) 75
HYPOAESTHESIA subjects affected / exposed occurrences (all)	46 / 532 (8.65%) 70	0 / 540 (0.00%) 0	40 / 541 (7.39%) 56
NEUROPATHY PERIPHERAL subjects affected / exposed occurrences (all)	35 / 532 (6.58%) 93	0 / 540 (0.00%) 0	62 / 541 (11.46%) 123
PARAESTHESIA subjects affected / exposed occurrences (all)	88 / 532 (16.54%) 143	74 / 540 (13.70%) 106	102 / 541 (18.85%) 241
PERIPHERAL MOTOR NEUROPATHY subjects affected / exposed occurrences (all)	28 / 532 (5.26%) 53	0 / 540 (0.00%) 0	0 / 541 (0.00%) 0
PERIPHERAL SENSORY NEUROPATHY subjects affected / exposed occurrences (all)	113 / 532 (21.24%) 219	93 / 540 (17.22%) 134	191 / 541 (35.30%) 447
SOMNOLENCE subjects affected / exposed occurrences (all)	31 / 532 (5.83%) 35	0 / 540 (0.00%) 0	51 / 541 (9.43%) 77
TREMOR			

subjects affected / exposed occurrences (all)	77 / 532 (14.47%) 110	73 / 540 (13.52%) 102	100 / 541 (18.48%) 169
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed occurrences (all)	237 / 532 (44.55%) 839	191 / 540 (35.37%) 586	219 / 541 (40.48%) 602
LEUKOPENIA			
subjects affected / exposed occurrences (all)	66 / 532 (12.41%) 345	59 / 540 (10.93%) 196	92 / 541 (17.01%) 438
LYMPHOPENIA			
subjects affected / exposed occurrences (all)	60 / 532 (11.28%) 219	43 / 540 (7.96%) 157	71 / 541 (13.12%) 364
NEUTROPENIA			
subjects affected / exposed occurrences (all)	194 / 532 (36.47%) 955	177 / 540 (32.78%) 647	325 / 541 (60.07%) 1854
THROMBOCYTOPENIA			
subjects affected / exposed occurrences (all)	111 / 532 (20.86%) 531	99 / 540 (18.33%) 318	132 / 541 (24.40%) 428
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed occurrences (all)	27 / 532 (5.08%) 34	0 / 540 (0.00%) 0	35 / 541 (6.47%) 42
Eye disorders			
CATARACT			
subjects affected / exposed occurrences (all)	84 / 532 (15.79%) 121	31 / 540 (5.74%) 40	0 / 541 (0.00%) 0
VISION BLURRED			
subjects affected / exposed occurrences (all)	30 / 532 (5.64%) 39	0 / 540 (0.00%) 0	0 / 541 (0.00%) 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed occurrences (all)	68 / 532 (12.78%) 95	40 / 540 (7.41%) 59	28 / 541 (5.18%) 34
ABDOMINAL PAIN UPPER			
subjects affected / exposed occurrences (all)	50 / 532 (9.40%) 65	34 / 540 (6.30%) 36	29 / 541 (5.36%) 32
CONSTIPATION			

subjects affected / exposed	233 / 532 (43.80%)	210 / 540 (38.89%)	282 / 541 (52.13%)
occurrences (all)	354	296	452
DIARRHOEA			
subjects affected / exposed	248 / 532 (46.62%)	205 / 540 (37.96%)	86 / 541 (15.90%)
occurrences (all)	656	367	107
DRY MOUTH			
subjects affected / exposed	38 / 532 (7.14%)	38 / 540 (7.04%)	62 / 541 (11.46%)
occurrences (all)	41	44	70
DYSPEPSIA			
subjects affected / exposed	59 / 532 (11.09%)	28 / 540 (5.19%)	36 / 541 (6.65%)
occurrences (all)	101	35	43
NAUSEA			
subjects affected / exposed	156 / 532 (29.32%)	127 / 540 (23.52%)	163 / 541 (30.13%)
occurrences (all)	261	187	233
TOOTHACHE			
subjects affected / exposed	28 / 532 (5.26%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	32	0	0
VOMITING			
subjects affected / exposed	97 / 532 (18.23%)	66 / 540 (12.22%)	104 / 541 (19.22%)
occurrences (all)	151	95	143
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	32 / 532 (6.02%)	30 / 540 (5.56%)	36 / 541 (6.65%)
occurrences (all)	36	39	41
ERYTHEMA			
subjects affected / exposed	35 / 532 (6.58%)	27 / 540 (5.00%)	0 / 541 (0.00%)
occurrences (all)	46	33	0
PRURITUS			
subjects affected / exposed	49 / 532 (9.21%)	49 / 540 (9.07%)	0 / 541 (0.00%)
occurrences (all)	62	72	0
RASH			
subjects affected / exposed	117 / 532 (21.99%)	129 / 540 (23.89%)	91 / 541 (16.82%)
occurrences (all)	230	238	161
Renal and urinary disorders			
RENAL FAILURE			

subjects affected / exposed	27 / 532 (5.08%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	30	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	110 / 532 (20.68%)	71 / 540 (13.15%)	67 / 541 (12.38%)
occurrences (all)	183	97	88
BACK PAIN			
subjects affected / exposed	175 / 532 (32.89%)	137 / 540 (25.37%)	115 / 541 (21.26%)
occurrences (all)	282	213	155
BONE PAIN			
subjects affected / exposed	83 / 532 (15.60%)	72 / 540 (13.33%)	58 / 541 (10.72%)
occurrences (all)	136	104	93
JOINT SWELLING			
subjects affected / exposed	29 / 532 (5.45%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	39	0	0
MUSCLE SPASMS			
subjects affected / exposed	115 / 532 (21.62%)	102 / 540 (18.89%)	61 / 541 (11.28%)
occurrences (all)	181	167	95
MUSCULAR WEAKNESS			
subjects affected / exposed	46 / 532 (8.65%)	34 / 540 (6.30%)	28 / 541 (5.18%)
occurrences (all)	61	51	43
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	63 / 532 (11.84%)	51 / 540 (9.44%)	39 / 541 (7.21%)
occurrences (all)	84	69	45
MUSCULOSKELETAL PAIN			
subjects affected / exposed	72 / 532 (13.53%)	58 / 540 (10.74%)	36 / 541 (6.65%)
occurrences (all)	106	75	42
MYALGIA			
subjects affected / exposed	31 / 532 (5.83%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	43	0	0
NECK PAIN			
subjects affected / exposed	43 / 532 (8.08%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	58	0	0
PAIN IN EXTREMITY			

subjects affected / exposed occurrences (all)	91 / 532 (17.11%) 140	65 / 540 (12.04%) 85	60 / 541 (11.09%) 78
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	90 / 532 (16.92%)	57 / 540 (10.56%)	42 / 541 (7.76%)
occurrences (all)	157	80	50
GASTROENTERITIS			
subjects affected / exposed	35 / 532 (6.58%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	41	0	0
INFLUENZA			
subjects affected / exposed	33 / 532 (6.20%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	38	0	0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	29 / 532 (5.45%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	51	0	0
NASOPHARYNGITIS			
subjects affected / exposed	90 / 532 (16.92%)	54 / 540 (10.00%)	33 / 541 (6.10%)
occurrences (all)	165	72	44
PNEUMONIA			
subjects affected / exposed	29 / 532 (5.45%)	34 / 540 (6.30%)	0 / 541 (0.00%)
occurrences (all)	37	38	0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	35 / 532 (6.58%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	54	0	0
RHINITIS			
subjects affected / exposed	31 / 532 (5.83%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	38	0	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	71 / 532 (13.35%)	48 / 540 (8.89%)	31 / 541 (5.73%)
occurrences (all)	123	69	42
URINARY TRACT INFECTION			
subjects affected / exposed	77 / 532 (14.47%)	59 / 540 (10.93%)	38 / 541 (7.02%)
occurrences (all)	133	72	52
Metabolism and nutrition disorders			

DECREASED APPETITE			
subjects affected / exposed	128 / 532 (24.06%)	115 / 540 (21.30%)	72 / 541 (13.31%)
occurrences (all)	219	156	94
HYPERGLYCAEMIA			
subjects affected / exposed	61 / 532 (11.47%)	50 / 540 (9.26%)	0 / 541 (0.00%)
occurrences (all)	142	158	0
HYPOCALCAEMIA			
subjects affected / exposed	60 / 532 (11.28%)	54 / 540 (10.00%)	30 / 541 (5.55%)
occurrences (all)	132	104	69
HYPOKALAEMIA			
subjects affected / exposed	104 / 532 (19.55%)	62 / 540 (11.48%)	38 / 541 (7.02%)
occurrences (all)	200	88	61
HYPOMAGNESAEMIA			
subjects affected / exposed	27 / 532 (5.08%)	0 / 540 (0.00%)	0 / 541 (0.00%)
occurrences (all)	54	0	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2008	1. Added pharmacoeconomic endpoint information 2. Advancements in fluorescence in situ hybridization (FISH) testing for cytogenetics testing caused a change in cytogenetic laboratories for North American and France to compare the latest cell sorting methodology with the current standard FISH performed by a central laboratory 3. Corrected errors in wording and units 4. Added testing of creatinine clearance at Day 1 of each cycle for dose escalation of lenalidomide and melphalan 5. Added emergency procedures 6. Clarified wording for antithrombotic treatment
07 November 2008	1. Clarification of efficacy assessments to be performed for Arms Rd, Rd18, and MPT during different phases of the study and when they were performed if there were interruptions in the cycle; 2. Clarification of study drug cycles and procedures for study drug during interruptions of any or all study drugs; 3. Clarification of the mandatory use of central laboratory results for subject eligibility and response assessments 4. Reduction of the washout period for a course of steroid treatment from 28 days to 14 days to allow subjects who were progressing rapidly access to the clinical trial; Addition of routine neurological examinations globally throughout the active treatment phase to provide additional neurological safety information on lenalidomide and thalidomide and as well as additional information when used in combination therapies; 5. Provided investigators with additional guidance on dose modification if a Grade 3 or greater lenalidomide-related hematologic toxicity occurred; 6. Addition of a dosing cap for melphalan to minimize toxicity in subjects weighing greater than 100 kg. Establishment of melphalan dosing criteria for subjects with renal impairment. 7. Allowance of a prednisone tapering per investigator discretion to prevent/minimize toxicity in subjects; 8. Updated and clarified AE and SAE reporting procedures; 9. Updated the risk management appendices for lenalidomide to reflect new animal data and the addition of this information to the subject guidance document as well as subject information sheets for FCBP, females not of childbearing potential, and males; 10. Clarification that only the descriptive system of the EQ-5D was to be used for QOL collection. The descriptive system of the EQ-5D, the 5-question piece of the EQ-5D, was used for converting the information into utilities for economic analysis; 11. Updated the IMWG response criteria for CR and PD.
01 April 2011	1. Added information on collection of data during PFS follow-up, specifically data on time to first progression following discontinuation of study medication, on subjects who discontinued early or for reasons other than progression of disease. Added sensitivity analysis based on additional PFS data as described above. 2. Further defined the data collection and analysis for the pharmacoeconomic endpoint 3. Added a secondary endpoint assessing improvement in CRAB criteria for subjects during active treatment phase 4. Added a dexamethasone taper for subjects with withdrawal toxicity 5. Required that Secondary Primary Malignancies (SPMs) be treated as SAEs and reported throughout the study duration from the time of signing the Informed Consent Document (ICD) to the time all subjects were followed for at least 5 years from randomization or had died

25 March 2012	1. In addition to the SPM reporting requirements outlined in Amendment No. 3, Amendment No. 4 included mandatory submission of samples and corresponding reports from screening and the SPM diagnosis for subjects who developed hematologic SPMs (including AML, ALL, CLL, MDS, or myeloproliferative disorders). For these hematologic SPMs, samples and reports were to be sent to an independent central reviewer for confirmation. Added mandatory submission of diagnostic reports (eg, pathology, cytogenetics, flow cytometry) from bone marrow aspirate smears collected at screening and from the SPM diagnosis to Celgene or a designee for central review and secondary confirmation for subjects with any SPM (solid tumors and hematologic malignancies). 2. Included collection of blood, bone marrow aspirate smears, saliva, and diagnostic tumor samples from SPM diagnoses for subjects who consented to optional collection of additional samples for exploratory biomarker studies. The purpose of the optional sample collection was to assess the mechanism of action of lenalidomide, to perform exploratory analyses to identify possible markers that correlate with response to lenalidomide, and additional studies to identify genetic aberrations possibly related to the development of SPMs in subjects treated with lenalidomide.
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25184863>

<http://www.ncbi.nlm.nih.gov/pubmed/27124703>

<http://www.ncbi.nlm.nih.gov/pubmed/26659916>

<http://www.ncbi.nlm.nih.gov/pubmed/27325857>

<http://www.ncbi.nlm.nih.gov/pubmed/25769541>

<http://www.ncbi.nlm.nih.gov/pubmed/28373701>