Clinical trial results:
A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma

Summary

EudraCT number	2010-019820-30
Trial protocol	BE GB DE GR IT CZ NL ES SE DK
Global end of trial date	28 August 2017

Results information

Result version number	v1 (current)
This version publication date	08 September 2018
First version publication date	08 September 2018

Trial information

Trial identification

Sponsor protocol code	CC-4047-MM-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01311687
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, NJ, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, ClinicalTrialDisclosure@celgene.com
Scientific contact	Lars Sternas, Celgene Corporation, +1 908 6739301, LSternas@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	28 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the efficacy of pomalidomide + low-dose dexamethasone (LD-dex) with that of high-dose dexamethasone (HD-dex) in subjects with refractory multiple myeloma (MM) or relapsed and refractory MM.

Protection of trial subjects:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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	Switzerland: 16
Country: Number of subjects enrolled	Germany: 69
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	France: 74
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Greece: 31
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Canada: 52
Worldwide total number of subjects	455
EEA total number of subjects	353

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	232
From 65 to 84 years	222
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 93 sites: 68 sites in Europe, 10 sites in Australia, 10 sites in Canada, 4 sites in Russia, and 1 site in the United States (US) from 18 March 2011 to 29 August 2017.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio. Treatment phase discontinuation occurred when a participant had confirmed progressive disease. Participants who did not progress but who were intolerant to treatment, or no longer wished to receive study treatment entered the progression-free survival (PFS) follow-up period until disease progression.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pomalidomide plus Low-Dose Dexamethasone

Arm description:

Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression.

Arm type	Experimental
Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	CC-4047
Other name	Pomalyst®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 mg pomalidomide capsules administered orally on Days 1-21 of each 28-day treatment cycle.

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

Dosage and administration details:

40 mg dexamethasone (or 20 mg for participants > 75 years of age) tablets administered orally Days 1, 8, 15, and 22 of each 28-day treatment cycle.

Arm title	High-Dose Dexamethasone

Arm description:

Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression.

Arm type	Active comparator

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

Dosage and administration details:

40 mg dexamethasone (or 20 mg for participants > 75 years of age) tablets administered orally on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day treatment cycle.

Number of subjects in period 1	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone
Started	302	153
Received Study Drug	300 [1]	150 [2]
Crossed-over to Pomalidomide	0 [3]	11 [4]
Completed	302	153

Notes:

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

Justification: Randomized subjects who received at least one dose of study drug (Completed indicates all subjects who had discontinued study drug).

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

Justification: After Amendment 4 participants still on HD-Dex treatment were permitted to crossover to pomalidomide treatment

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

Justification: Not applicable to participants in this arm initially randomized to receive pomalidomide

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

Justification: Only includes participants who discontinued treatment prior to disease progression who entered the PFS follow-up period.

Period 2

Period 2 title	PFS Follow-up Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pomalidomide plus Low-Dose Dexamethasone

Arm description:

Participants who received pomalidomide and low-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	High-Dose Dexamethasone

Arm description:

Participants who received high-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[5]	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone
Started	11	8
Completed	11	8

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Randomized subjects who received at least one dose of study drug (Completed indicates all subjects who had discontinued study drug).

Baseline characteristics

Reporting groups	
Reporting group title	Pomalidomide plus Low-Dose Dexamethasone
Reporting group description:	
Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression.	
Reporting group title	High-Dose Dexamethasone
Reporting group description:	
Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression.	

Reporting group values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone	Total
Number of subjects	302	153	455
Age, Customized			
Stratification Factor 1			
Units: Subjects			
≤ 75 Years Old	278	141	419
> 75 Years Old	24	12	36
Age Continuous			
Units: years			
arithmetic mean	63.6	63.7	
standard deviation	± 9.33	± 9.56	-
Sex: Female, Male			
Units: Subjects			
Female	121	66	187
Male	181	87	268
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	27	14	41
Not Hispanic or Latino	228	104	332
Unknown or Not Reported	47	35	82
Race/Ethnicity, Customized			
Units: Subjects			
Asian	4	0	4
Black or African American	4	3	7
White	244	113	357
Other	2	2	4
Not collected	48	35	83
Stratification Factor 2: Disease Population			
Disease Population Group 1 is defined as refractory patients who have progressed on or within 60 days of both lenalidomide and bortezomib based treatments. Disease Population Group 2 is defined as relapsed and refractory patients who achieved at least a partial response (PR) and progressed within 6 months after stopping treatment with lenalidomide and/or bortezomib. Disease Population Group 3 is defined as refractory/intolerant patients who developed intolerance/toxicity after a minimum of 2 cycles of bortezomib.			
Units: Subjects			

Disease Population Group 1	249	125	374
Disease Population Group 2	8	5	13
Disease Population Group 3	45	23	68
Stratification Factor 3: Number of Prior Anti-MM Therapies Units: Subjects			
2 Prior Anti-MM Therapies	17	8	25
>2 Prior Anti-MM Therapies	285	145	430
Multiple Myeloma Stage before Study Entry			
The International Staging System divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Stage I: Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L); Stage II: Neither stage I or III, meaning that either: The beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), OR The albumin is below 3.5 while the beta-2 microglobulin is less than 3.5 Stage III: Serum beta-2 microglobulin is greater than 5.5.			
Units: Subjects			
Stage I	81	36	117
Stage II	115	56	171
Stage III	92	53	145
Missing	14	8	22
Time from First Pathologic Diagnosis Units: years			
arithmetic mean	6.2	6.5	
standard deviation	± 4.02	± 3.63	-

End points

End points reporting groups

Reporting group title	Pomalidomide plus Low-Dose Dexamethasone

Reporting group description:

Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression.

Reporting group title	High-Dose Dexamethasone

Reporting group description:

Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression.

Reporting group title	Pomalidomide plus Low-Dose Dexamethasone

Reporting group description:

Participants who received pomalidomide and low-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period.

Reporting group title	High-Dose Dexamethasone

Reporting group description:

Participants who received high-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period.

Subject analysis set title	HD-Dex / Pomalidomide
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants initially randomized to high-dose dexamethasone (HD-Dex) crossed over to receive 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle, with or without low-dose dexamethasone (40 mg for participants ≤ 75 years or 20 mg for participants > 75 years of age, administered orally once per day on Days 1, 8, 15, and 22 of each 28-day cycle) at the discretion of the investigator. Data include AEs that occurred after cross-over to pomalidomide.

Primary: Progression-free Survival (PFS) - Primary Analysis

End point title	Progression-free Survival (PFS) - Primary Analysis

End point description:

Progression-free survival was calculated as the time from randomization to disease progression as determined by the Independent Response Adjudication Committee based on the International Myeloma Working Group Uniform Response criteria (IMWG), or death on study, whichever occurred earlier. Progressive disease required 1 of the following: • Increase of ≥ 25% from nadir in: o Serum M-component (absolute increase ≥ 0.5 g/dl); o Urine M-component (absolute increase ≥ 200 mg/24 hours); o Bone marrow plasma cell percentage (absolute % ≥ 10%); • Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 07 September 2012. Maximum duration of follow-up for PFS assessments was 57 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: weeks				
median (confidence interval 95%)	15.7 (13.0 to 20.1)	8.0 (7.0 to 9.0)		

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival
Comparison groups	Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.59

Notes:

[1] - Stratified by age, disease population, and prior number of anti myeloma therapy.

Primary: Progression-free Survival (PFS) with a Later Cut-off Date

End point title	Progression-free Survival (PFS) with a Later Cut-off Date

End point description:

Progression-free survival was calculated as the time from randomization to disease progression as determined by the Independent Response Adjudication Committee based on the International Myeloma Working Group Uniform Response criteria (IMWG), or death on study, whichever occurred earlier. Progressive disease requires 1 of the following: • Increase of ≥ 25% from nadir in: o Serum M-component (absolute increase ≥ 0.5 g/dl); o Urine M-component (absolute increase ≥ 200 mg/24 hours); o Bone marrow plasma cell percentage (absolute % ≥ 10%); • Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease.

End point type	Primary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum duration of follow-up for PFS assessments was 74 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: weeks				
median (confidence interval 95%)	16.0 (13.0 to 19.6)	8.1 (7.1 to 9.4)		

Statistical analyses

Statistical analysis title	Analysis of Progresion-free Survival
Comparison groups	Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.61

Notes:

[2] - Stratified by age, disease population, and prior number of anti myeloma therapy.

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. A serious AE is any AE occurring at any dose that: • Resulted in death; • Was life-threatening; • Required or prolonged existing inpatient hospitalization; • Resulted in persistent or significant disability/incapacity; • Was a congenital anomaly/birth defect; • Constitutes an important medical event. The Investigator assessed the relationship of each AE to study drug and graded the severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0): Grade 1 = Mild (no limitation in activity or intervention required); Grade 2 = Moderate (some limitation in activity; no/minimal medical intervention required); Grade 3 = Severe (marked limitation in activity; medical intervention required, hospitalization possible); Grade 4 = Life-threatening; Grade 5 = Death.

End point type	Secondary

End point timeframe:

From first dose of study drug through to 30 days after the last dose as of the end of the study (29 August 2017); maximum time on treatment was 297, 269, and 239 weeks in the Pomalidomide + LD-Dex, HD-Dex, and cross-over groups respectively.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone	HD-Dex / Pomalidomide	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	300[3]	150[4]	11	
Units: participants				
Any adverse event	298	149	11	
Grade 3-4 adverse events	266	127	8	
AE related to pomalidomide	251	0	11	
AE related to dexamethasone	205	115	5	
AE related to either study drug	271	115	11	
Grade 3-4 AE related to pomalidomide	199	0	6	
Grade 3-4 AE related to dexamethasone	114	70	2	
Grade 3-4 AE related to either study drug	212	70	6	
Grade 5 adverse events	46	21	1	
Serious adverse events (SAEs)	195	80	4	
SAE related to pomalidomide|	89	0	1	
SAE related to dexamethasone	73	36	0	
SAE related to either study drug	98	36	1	
SAE leading to discontinuation of pomalidomide	20	0	1	
SAE leading to discontinuation of dexamethasone	20	14	1	
SAE leading to discontinuation of either study dru	23	14	1	
AE leading to discontinuation of pomalidomide	30	0	1	
AE leading to discontinuation of dexamethasone	34	16	1	
AE leading to discontinuation of either study drug	38	16	1	

Notes:

[3] - Randomized participants who received at least one dose of study drug

[4] - Randomized participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - Primary Analysis

End point title	Overall Survival - Primary Analysis

End point description:

Overall survival is calculated as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 07 September 2012. Maximum time on follow-up for survival was 70 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: weeks				
median (confidence interval 95%)	99999 (48.1 to 99999)	34.0 (23.4 to 39.9)		

Statistical analyses

Statistical analysis title	Analysis of Overal Survival
Comparison groups	Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.74

Secondary: Overall Survival with a Later Cut-off Date

End point title	Overall Survival with a Later Cut-off Date

End point description:

Overall survival is calculated as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up for survival was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: weeks				
median (confidence interval 95%)	54.0 (45.3 to	34.9 (29.9 to		

66.4)	39.1)

Statistical analyses

Statistical analysis title	Ananlysis of Overall Survival
Comparison groups	Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.92

Secondary: Overall Survival Based on the Final Dataset

End point title	Overall Survival Based on the Final Dataset

End point description:

Overall survival is calculated as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 29 August 2017. Maximum time on follow-up for survival was 324 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: weeks				
median (confidence interval 95%)	56.1 (47.7 to 67.4)	35.3 (29.9 to 39.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Objective Response According to International Myeloma Working Group (IMWG) Uniform Response Criteria

End point title	Percentage of Participants with an Objective Response According to International Myeloma Working Group (IMWG) Uniform Response Criteria

End point description:

Objective response is defined as a best overall response of stringent complete response (SCR), complete response (CR), very good partial response (VGPR) or partial response (PR) based on the Independent Response Adjudication Committee: SCR: CR and normal free light chain (FLC) ratio and no clonal cells in bone marrow; CR: Negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow; VGPR: 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; PR: ≥ 50% reduction of serum M-Protein and reduction in urinary M-protein by ≥ 90% or to < 200 mg/24 hours. In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: percentage of participants				
number (not applicable)	23.5	3.9		

Statistical analyses

Statistical analysis title	Analysis of Objective Response According to IMWG
Comparison groups	Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	7.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.19
upper limit	17.77

Secondary: Percentage of Participants with Objective Response According to European Group for Blood and Marrow Transplantation (EBMT) Criteria

End point title	Percentage of Participants with Objective Response According to European Group for Blood and Marrow Transplantation (EBMT) Criteria

End point description:

Objective response defined as a best overall response of complete response (CR) or partial response (PR) based on the Independent Response Adjudication Committee: CR requires all of the following: - Absence of original monoclonal paraprotein in serum and urine by immunofixation maintained at least 42 days. - <5% plasma cell in bone marrow aspirate and on bone marrow biopsy, if performed. - No increase in size or number of lytic bone lesions. - Disappearance of soft tissue plasmacytomas. PR requires all of the following: - ≥ 50% reduction in level of serum monoclonal paraprotein, maintained at least 42 days. - Reduction in 24-hour urinary light chain extraction by ≥ 90% or to < 200 mg, maintained at least 42 days. - For patients with non-secretory myeloma, ≥ 50% reduction in plasma cells in bone marrow aspirate and on biopsy, if performed, for at least 42 days. - ≥ 50% reduction in the size of soft tissue plasmacytomas. - No increase in size or number of lytic bone lesions.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: percentage of participants				
number (not applicable)	22.2	3.3		

Statistical analyses

Statistical analysis title	Analysis of Objective Response According to EBMT
Comparison groups	Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	8.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.32
upper limit	21.42

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression (TTP) is calculated as the time from randomization to the first documented progression confirmed by a blinded, independent Response Adjudication Committee and based on the International Myeloma Working Group Uniform Response criteria (IMWG). Progressive disease requires 1 of the following: • Increase of ≥ 25% from nadir in: o Serum M-component (absolute increase ≥ 0.5 g/dl); o Urine M-component (absolute increase ≥ 200 mg/24 hours); o Bone marrow plasma cell percentage (absolute % ≥ 10%); • Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302	153		
Units: weeks				
median (confidence interval 95%)	20.0 (16.1 to 24.0)	9.0 (8.0 to 10.9)		

Statistical analyses

Statistical analysis title	Analysis of Time to Progression
Comparison groups	High-Dose Dexamethasone v Pomalidomide plus Low-Dose Dexamethasone
Number of subjects included in analysis	455
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.59

Notes:

[5] - Stratified by age, diseases population, and prior number of anti myeloma therapy.

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response is calculated as the time from randomization to the initial documented response (partial response or better) based on IMWG criteria. SCR: CR and normal free light chain (FLC) ratio and no clonal cells in bone marrow; CR: Negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow; VGPR: 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; PR: ≥ 50% reduction of serum M-Protein and reduction 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 is also required.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[6]	6[7]		
Units: weeks				
median (full range (min-max))	8.1 (4.0 to 48.0)	10.5 (4.1 to 42.1)		

Notes:

[6] - Randomized participants with a response

[7] - Randomized participants with a response

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (calculated for responders only) is defined as time from the initial documented response (partial response or better) to confirmed disease progression, based on IMWG criteria assessed by the Independent Response Adjudication Committee.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[8]	6[9]		
Units: weeks				
median (confidence interval 95%)	35.1 (28.4 to 52.9)	28.1 (20.1 to 37.1)		

Notes:

[8] - Randomized participants with a response

[9] - Randomized participants with a response

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the First Hemoglobin Improvement

End point title	Time to the First Hemoglobin Improvement

End point description:

Time to increased hemoglobin, defined as the time from randomization to at least one category improvement from Baseline in common terminology criteria for adverse events (CTCAE) grade for hemoglobin level. Hemoglobin categories are: 1) Normal; 2) CTCAE Grade 1: < lower limit of normal (LLN) to 10.0 g/dL; 3) CTCAE Grade 2: < 10.0 to <8.0 g/dL. Participants with CTCAE Grade 3 anemia or worse at Baseline were excluded from the study.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[10]	50[11]		
Units: weeks				
median (full range (min-max))	3.4 (1.1 to 49.3)	1.3 (0.9 to 24.3)		

Notes:

[10] - Randomized participants with improvement in hemoglobin during the study

[11] - Randomized participants with improvement in hemoglobin during the study

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement in Bone Pain

End point title	Time to Improvement in Bone Pain

End point description:

Time to improvement in bone pain is defined as the time from randomization to at least one category improvement from Baseline in bone pain category. Bone pain was categorized (from best to worst) according to answers to the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for patients with Multiple Myeloma Module (QLQ-MY20), Question 1, "Have

you had bone aches or pain?": 1) Not at all, 2) A little, 3) Quite a bit, or 4) Very much.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[12]	37[13]		
Units: weeks				
median (full range (min-max))	5.7 (3.7 to 88.6)	4.1 (3.7 to 27.3)		

Notes:

[12] - Randomized participants with improvement in bone pain

[13] - Randomized participants with improvement in bone pain

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement in Renal Function

End point title	Time to Improvement in Renal Function

End point description:

Time to improvement in renal function is defined as the time from randomization to at least one category improvement from Baseline in renal function. Renal Function was categorized as (from best to worst): • Normal: creatinine clearance ≥80 mL/min; • Grade 1: creatinine clearance ≥60 to <80 mL/min; • Grade 2 : creatinine clearance ≥45 to < 60 mL/min. Participants with creatinine clearance < 45 mL/min at baseline were be excluded from the study.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[14]	45[15]		
Units: weeks				
median (full range (min-max))	4.6 (3.3 to 45.6)	4.1 (3.3 to 28.1)		

Notes:

[14] - Randomized participants with improvement in renal function

[15] - Randomized participants with improvement in renal function

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Time to Improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

Time to improvement in ECOG performance status defined as the time from randomization until at least a one category improvement from Baseline in ECOG performance status score. The categories of the ECOG Performance Status Scale are as follows: -0: Fully active, able to carry on all pre-disease performance without restriction; -1: Restricted in physically strenuous activity but ambulatory and able to carry our work of a light or sedentary nature, e.g., light housework, office work; -2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. Patients with a score of 3, 4 or 5 were excluded from participating in the study.

End point type	Secondary

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[16]	18[17]		
Units: weeks				
median (full range (min-max))	8.1 (4.1 to 44.1)	4.3 (4.1 to 33.7)		

Notes:

[16] - Randomized participants with improvement in ECOG performance status during the study

[17] - Randomized participants with improvement in ECOG performance status during the study

Statistical analyses

No statistical analyses for this end point

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

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. The Patient Reported Outcomes (PRO) population includes randomized participants with 1 active treatment and 1 PRO measurement item completed. Only participants with available data at Baseline and each time point are included.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[18]	144[19]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=209, 91)	0.52 (± 23.01)	-3.75 (± 24.10)		
Cycle 3, Day 1 (N=175, 53)	2.67 (± 24.97)	-2.36 (± 21.08)		
Cycle 4, Day 1 (N=157, 33)	0.80 (± 24.62)	-3.03 (± 22.42)		
Cycle 5 Day 1 (N=130, 27)	0.51 (± 26.81)	0.00 (± 27.44)		
Cycle 6, Day 1 (N=116, 18)	-2.51 (± 25.57)	-0.93 (± 17.59)		

Notes:

[18] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[19] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

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

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.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[20]	144[21]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=210, 91)	-2.32 (± 18.25)	-3.96 (± 18.35)		
Cycle 3, Day 1 (N=177, 53)	-0.56 (± 19.86)	-9.69 (± 16.67)		
Cycle 4, Day 1 (N=159, 33)	0.17 (± 20.25)	-8.08 (± 13.31)		
Cycle 5 Day 1 (N=132, 27)	0.91 (± 19.92)	-5.43 (± 19.31)		
Cycle 6, Day 1 (N=118, 18)	0.54 (± 21.30)	-4.81 (± 14.24)		

Notes:

[20] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed
[21] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

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

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.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[22]	144[23]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=210, 91)	1.22 (± 21.44)	-2.87 (± 21.57)		

Cycle 3, Day 1 (N=176, 53)	2.40 (± 20.36)	-5.66 (± 25.36)		
Cycle 4, Day 1 (N=158, 33)	2.44 (± 21.05)	-6.31 (± 23.48)		
Cycle 5 Day 1 (N=131, 27)	1.91 (± 21.97)	-8.64 (± 23.17)		
Cycle 6, Day 1 (N=117, 18)	0.19 (± 22.30)	-4.17 (± 13.18)		

Notes:

[22] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed
[23] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

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

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 reduction in fatigue (i.e. improvement in symptom) and positive values indicate increases in fatigue (i.e. worsening of symptom).

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[24]	144[25]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=210, 91)	2.43 (± 27.39)	4.03 (± 25.37)		
Cycle 3, Day 1 (N=177, 53)	3.26 (± 27.66)	7.76 (± 23.73)		
Cycle 4, Day 1 (N=159, 33)	1.71 (± 26.21)	9.43 (± 28.88)		
Cycle 5 Day 1 (N=132, 27)	0.21 (± 28.41)	9.47 (± 23.00)		
Cycle 6, Day 1 (N=118, 18)	0.99 (± 31.13)	10.49 (± 16.38)		

Notes:

[24] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed
[25] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

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

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 reductions in pain (i.e. improvement in symptom) and positive values indicate increases in pain (i.e. worsening of symptom).

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[26]	144[27]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=210, 92)	-2.70 (± 25.74)	0.36 (± 25.32)		
Cycle 3, Day 1 (N=177, 53)	-3.58 (± 29.62)	2.83 (± 25.47)		
Cycle 4, Day 1 (N=159, 33)	-2.41 (± 30.52)	3.03 (± 25.84)		
Cycle 5 Day 1 (N=132, 27)	-1.64 (± 28.00)	2.47 (± 31.59)		
Cycle 6, Day 1 (N=118, 18)	-2.40 (± 30.99)	10.19 (± 23.67)		

Notes:

[26] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[27] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms

End point title	Change from Baseline in the European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms

End point description:

The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) is a 20-question tool used in clinical research to assess health-

related quality of life in multiple myeloma patients. The QLQ-MY20 includes four domains (Disease Symptoms, Side-Effects of Treatment, Body Image and Future Perspective). The EORTC QLQ-MY20 Disease Symptoms Scale is scored between 0 and 100, with a high score reflecting a higher level of symptoms. Negative change from Baseline values indicate reduction (i.e. improvement) in symptoms and positive values indicate increase (i.e. worsening) of symptoms.

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[28]	144[29]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=218, 99)	-0.50 (± 16.51)	-1.07 (± 17.78)		
Cycle 3, Day 1 (N=180, 56)	-1.36 (± 19.51)	0.97 (± 19.93)		
Cycle 4, Day 1 (N=161, 37)	-1.15 (± 19.54)	1.35 (± 16.94)		
Cycle 5 Day 1 (N=135, 30)	-0.53 (± 17.39)	1.48 (± 17.56)		
Cycle 6, Day 1 (N=115, 21)	0.60 (± 19.64)	2.12 (± 13.43)		

Notes:

[28] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed
[29] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-MY20 Side Effects Domain

End point title	Change from Baseline in the EORTC QLQ-MY20 Side Effects Domain

End point description:

The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) is a 20-question tool used in clinical research to assess health-related quality of life in multiple myeloma patients. The QLQ-MY20 includes four domains (Disease Symptoms, Side-Effects of Treatment, Body Image and Future Perspective). The EORTC QLQ-MY20 Side Effects Scale is scored between 0 and 100, with a high score reflecting a higher level of symptoms. Negative change from Baseline values indicate reduction in side effects (i.e.improvement in symptom) and positive values indicate increase in side effects (i.e. worsening of symptom).

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[30]	144[31]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=218, 99)	2.71 (± 13.90)	2.61 (± 13.34)		
Cycle 3, Day 1 (N=180, 55)	3.26 (± 13.72)	5.35 (± 12.27)		
Cycle 4, Day 1 (N=161, 37)	3.73 (± 14.47)	7.46 (± 11.61)		
Cycle 5 Day 1 (N=135, 30)	4.74 (± 14.45)	6.89 (± 10.32)		
Cycle 6, Day 1 (N=115, 21)	4.55 (± 15.76)	7.30 (± 9.35)		

Notes:

[30] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[31] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the European Quality of Life-5 Dimensions (EQ-5D) Utility Index Score

End point title	Change from baseline in the European Quality of Life-5 Dimensions (EQ-5D) Utility Index Score

End point description:

EQ-5D is a self-administered questionnaire that assesses health-related quality of life (QOL). 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 an EQ-5D score of 1.00 equals “perfect health”, a score of 0 equals “death” and a score of -0.59 equals worst imaginable health state. A positive change from Baseline score indicates improvement in health status. A negative change from Baseline score indicates worsening in health status. Negative scores represent the possible though unlikely situation that a patient's QOL is worse than death, i.e. they would rather be dead than living with that QOL

End point type	Secondary

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[32]	144[33]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cycle 2, Day 1 (N=198, 89)	-0.03 (± 0.28)	-0.02 (± 0.23)		
Cycle 3, Day 1 (N=167, 52)	0.01 (± 0.29)	-0.06 (± 0.27)		
Cycle 4, Day 1 (N=146, 33)|	0.04 (± 0.31)	-0.07 (± 0.29)		
Cycle 5, Day 1 (N=125, 25)	0.01 (± 0.32)	-0.04 (± 0.26)		
Cycle 6, Day 1 (N=108, 18)	0.03 (± 0.31)	-0.12 (± 0.19)		

Notes:

[32] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed
[33] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Worsening of Quality of Life (QOL) Domains

End point title	Time to First Worsening of Quality of Life (QOL) Domains

End point description:

Time to worsening in quality of life domains was calculated as the time from Baseline to the first worsened minimally important difference (MID), defined as the smallest change in a QOL score considered important to patients that would lead the patient or clinician to consider a change in therapy. MID thresholds were calculated in Standard Error of Measurement (SEM) units using the Baseline QOL data. Based on the MID, participants were classified as worsened according to the following: For the EORTC QLQ-C30 global health status and functional scales and the EQ-5D health utility score, participants were classified as worsened if their change from Baseline score was less than -1 SEM. For the EORTC QLQ-C30 symptom scores (fatigue and pain) and EORTC QLQ-MY20 disease symptoms and side effects scales, participants were classified as worsened if their change from Baseline score was greater than 1 SEM. See previous outcome measures for definitions of each scale.

End point type	Secondary

End point timeframe:

Assessed on Day 1 of the first 6 treatment cycles.

End point values	Pomalidomide plus Low-Dose Dexamethasone	High-Dose Dexamethasone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[34]	144[35]		
Units: days				
median (confidence interval 95%)				
Global Health Status	71 (60 to 92)	57 (36 to 91)		
Physical Functioning	128 (92 to 225)	67 (57 to 106)		
Emotional Functioning	146 (120 to 259)	85 (57 to 124)		
Fatigue	58 (57 to 85)	57 (46 to 67)		
Pain	92 (86 to 147)	85 (62 to 337)		
Disease Symptoms	127 (92 to 155)	106 (67 to 141)		
Side Effects of Treatment	90 (78 to 123)	85 (58 to 113)		
Health Utility	225 (123 to 338)	162 (85 to 99999)		

Notes:

[34] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed
[35] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through to 30 days after the last dose as of the end of the study (29 August 2017); maximum time on treatment was 297, 269, and 239 weeks in the Pomalidomide + LD-Dex, HD-Dex, and cross-over groups respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Pomalidomide Plus Low-Dose Dexamethasone

Reporting group description:

Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression.

Reporting group title	High-Dose Dexamethasone (BEFORE CROSSOVER)

Reporting group description:

Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression, or until cross-over to pomalidomide. Data are up to the time of cross-over.

Reporting group title	High Dose Dexamethasone/Pomalidomide (AFTER CROSSOVER)

Reporting group description:

Participants initially randomized to high-dose dexamethasone (HD-Dex) crossed over to receive 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle, with or without low-dose dexamethasone (40 mg for participants ≤ 75 years or 20 mg for participants > 75 years of age, administered orally once per day on Days 1, 8, 15, and 22 of each 28-day cycle) at the discretion of the investigator. Data include AEs that occurred after cross-over to pomalidomide.

Serious adverse events	Pomalidomide Plus Low-Dose Dexamethasone	High-Dose Dexamethasone (BEFORE CROSSOVER)	High Dose Dexamethasone/Pomalidomide (AFTER CROSSOVER)
Total subjects affected by serious adverse events			
subjects affected / exposed	195 / 300 (65.00%)	80 / 150 (53.33%)	4 / 11 (36.36%)
number of deaths (all causes)	252	124	8
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 300 (1.00%)	0 / 150 (0.00%)	0 / 11 (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
Plasma cell leukaemia			

subjects affected / exposed	1 / 300 (0.33%)	2 / 150 (1.33%)	0 / 11 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Plasmacytoma			
subjects affected / exposed	3 / 300 (1.00%)	1 / 150 (0.67%)	0 / 11 (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
Prostate cancer stage IV			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Tumour pain			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Vascular disorders			
Axillary vein thrombosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Circulatory collapse			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Deep vein thrombosis			

subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Hypertension			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 crisis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Hypotension			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Asthenia			
subjects affected / exposed	1 / 300 (0.33%)	2 / 150 (1.33%)	0 / 11 (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
Catheter site haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	3 / 300 (1.00%)	0 / 150 (0.00%)	0 / 11 (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
General physical health deterioration			

subjects affected / exposed	26 / 300 (8.67%)	12 / 150 (8.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 34	1 / 18	0 / 0
deaths causally related to treatment / all	0 / 17	0 / 6	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Malaise			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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 organ dysfunction syndrome			
subjects affected / exposed	4 / 300 (1.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Oedema peripheral			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Pyrexia			

subjects affected / exposed	26 / 300 (8.67%)	7 / 150 (4.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	15 / 35	4 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Atelectasis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cough			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Dyspnoea			
subjects affected / exposed	9 / 300 (3.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	5 / 11	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	3 / 300 (1.00%)	2 / 150 (1.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			

subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Oropharyngeal pain			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Pneumonitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Productive cough			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Pulmonary embolism			
subjects affected / exposed	5 / 300 (1.67%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 300 (0.00%)	2 / 150 (1.33%)	0 / 11 (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
Respiratory failure			
subjects affected / exposed	3 / 300 (1.00%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Aggression			

subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Bradyphrenia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Confusional state			
subjects affected / exposed	3 / 300 (1.00%)	3 / 150 (2.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 300 (0.33%)	2 / 150 (1.33%)	0 / 11 (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
Blood immunoglobulin M increased			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
C-reactive protein increased			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Platelet count decreased			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Femur fracture			
subjects affected / exposed	5 / 300 (1.67%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Humerus fracture			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (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 vertebral fracture			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Pelvic fracture			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Post procedural haematoma			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Spinal compression fracture			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Subdural haematoma			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Atrial fibrillation			
subjects affected / exposed	7 / 300 (2.33%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	3 / 12	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Atrial tachycardia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac amyloidosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	4 / 300 (1.33%)	2 / 150 (1.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 6	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Myocardial infarction			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Sinus bradycardia			

subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Sinus node dysfunction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Tachycardia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Ventricular tachycardia			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (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
Cognitive disorder			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Coma			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Depressed level of consciousness			

subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Dizziness			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Dyspraxia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Encephalopathy			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Epilepsy			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Headache			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Hemiparesis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Loss of consciousness			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Neurological decompensation			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Parkinson's disease			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Partial seizures			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Presyncope			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Radiculopathy			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Seizure			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Spinal cord compression			

subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Vertigo CNS origin			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 300 (3.33%)	7 / 150 (4.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	6 / 11	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood disorder			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Febrile neutropenia			
subjects affected / exposed	19 / 300 (6.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	34 / 40	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Hyperviscosity syndrome			
subjects affected / exposed	1 / 300 (0.33%)	2 / 150 (1.33%)	0 / 11 (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
Neutropenia			
subjects affected / exposed	10 / 300 (3.33%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	9 / 10	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 300 (0.67%)	2 / 150 (1.33%)	0 / 11 (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
Thrombocytopenia			
subjects affected / exposed	6 / 300 (2.00%)	4 / 150 (2.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	3 / 6	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Constipation			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Dental caries			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 300 (0.67%)	2 / 150 (1.33%)	0 / 11 (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
Enteritis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Large intestine perforation			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Melaena			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Necrotising colitis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Oesophagitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Papilla of Vater stenosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Stomatitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Vomiting			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Hepatobiliary disorders			
Cholestasis			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Gallbladder perforation			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 mass			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	11 / 300 (3.67%)	7 / 150 (4.67%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	1 / 19	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Crush syndrome			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 / 300 (2.67%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	3 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	4 / 300 (1.33%)	2 / 150 (1.33%)	0 / 11 (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
Urinary retention			

subjects affected / exposed	3 / 300 (1.00%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	8 / 300 (2.67%)	2 / 150 (1.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 9	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	10 / 300 (3.33%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 compression			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Joint swelling			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	0 / 300 (0.00%)	2 / 150 (1.33%)	0 / 11 (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
Musculoskeletal chest pain			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Myalgia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Myopathy			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Osteoarthritis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Pain in extremity			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Pain in jaw			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Pathological fracture			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (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
Spinal pain			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Acute sinusitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Anal abscess			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Aspergillus infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Bacteraemia			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (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
Bacterial diarrhoea			

subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Bacterial infection			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Bacterial sepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Bronchitis			
subjects affected / exposed	8 / 300 (2.67%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 8	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Cellulitis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Cytomegalovirus chorioretinitis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Device related infection			

subjects affected / exposed	3 / 300 (1.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Diverticulitis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Enterobacter infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Enterobacter sepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Erysipelas			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	3 / 300 (1.00%)	0 / 150 (0.00%)	0 / 11 (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
Escherichia urinary tract infection			

subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Gastroenteritis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Herpes zoster			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	3 / 300 (1.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Intervertebral discitis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Klebsiella sepsis			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Listeria sepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Lower respiratory tract infection			
subjects affected / exposed	6 / 300 (2.00%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	5 / 7	2 / 6	0 / 1
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 0
Lung infection			
subjects affected / exposed	5 / 300 (1.67%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	4 / 9	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Meningitis cryptococcal			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Neutropenic sepsis			
subjects affected / exposed	3 / 300 (1.00%)	0 / 150 (0.00%)	0 / 11 (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
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Ophthalmic herpes zoster			

subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Pneumococcal bacteraemia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	3 / 300 (1.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	57 / 300 (19.00%)	14 / 150 (9.33%)	2 / 11 (18.18%)
occurrences causally related to treatment / all	38 / 71	11 / 18	0 / 2
deaths causally related to treatment / all	3 / 5	1 / 3	0 / 0
Pneumonia bacterial			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Pneumonia pneumococcal			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Pneumonia pseudomonal			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	0 / 11 (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
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 bacteraemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Pseudomonal sepsis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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 syncytial virus infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 tract infection			
subjects affected / exposed	4 / 300 (1.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella sepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Sepsis			

subjects affected / exposed	7 / 300 (2.33%)	3 / 150 (2.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	3 / 11	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 2	2 / 2	0 / 0
Sepsis syndrome			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Septic arthritis streptococcal			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Septic shock			
subjects affected / exposed	4 / 300 (1.33%)	6 / 150 (4.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 5	3 / 6	0 / 0
deaths causally related to treatment / all	1 / 1	2 / 5	0 / 0
Sialoadenitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Sinusitis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	0 / 11 (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
Skin infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Streptococcal infection			

subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Streptococcal sepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Subdural empyema			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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 infection			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Upper respiratory tract infection			
subjects affected / exposed	7 / 300 (2.33%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	2 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 300 (0.00%)	5 / 150 (3.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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	1 / 300 (0.33%)	0 / 150 (0.00%)	0 / 11 (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
Decreased appetite			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Dehydration			
subjects affected / exposed	4 / 300 (1.33%)	2 / 150 (1.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	13 / 300 (4.33%)	5 / 150 (3.33%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 17	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 300 (0.67%)	3 / 150 (2.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	0 / 11 (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
Hypokalaemia			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	0 / 11 (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
Hyponatraemia			

subjects affected / exposed	4 / 300 (1.33%)	0 / 150 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pomalidomide Plus Low-Dose Dexamethasone	High-Dose Dexamethasone (BEFORE CROSSOVER)	High Dose Dexamethasone/Pomalidomide (AFTER CROSSOVER)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	291 / 300 (97.00%)	143 / 150 (95.33%)	11 / 11 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	9 / 300 (3.00%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	10	2	1
Hot flush			
subjects affected / exposed	2 / 300 (0.67%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	2	2	1
Hypotension			
subjects affected / exposed	13 / 300 (4.33%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	14	4	1
Thrombophlebitis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	53 / 300 (17.67%)	25 / 150 (16.67%)	1 / 11 (9.09%)
occurrences (all)	76	42	1
Chest pain			
subjects affected / exposed	11 / 300 (3.67%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	12	4	2
Chills			
subjects affected / exposed	18 / 300 (6.00%)	2 / 150 (1.33%)	0 / 11 (0.00%)
occurrences (all)	20	2	0
Fatigue			

subjects affected / exposed	103 / 300 (34.33%)	40 / 150 (26.67%)	3 / 11 (27.27%)
occurrences (all)	200	82	5
General physical health deterioration			
subjects affected / exposed	17 / 300 (5.67%)	5 / 150 (3.33%)	0 / 11 (0.00%)
occurrences (all)	19	5	0
Influenza like illness			
subjects affected / exposed	3 / 300 (1.00%)	1 / 150 (0.67%)	2 / 11 (18.18%)
occurrences (all)	4	1	2
Malaise			
subjects affected / exposed	10 / 300 (3.33%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	11	1	1
Oedema			
subjects affected / exposed	9 / 300 (3.00%)	7 / 150 (4.67%)	1 / 11 (9.09%)
occurrences (all)	9	10	1
Oedema peripheral			
subjects affected / exposed	51 / 300 (17.00%)	15 / 150 (10.00%)	3 / 11 (27.27%)
occurrences (all)	79	18	4
Pyrexia			
subjects affected / exposed	74 / 300 (24.67%)	31 / 150 (20.67%)	3 / 11 (27.27%)
occurrences (all)	117	43	4
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	64 / 300 (21.33%)	15 / 150 (10.00%)	1 / 11 (9.09%)
occurrences (all)	85	16	1
Dyspnoea			
subjects affected / exposed	60 / 300 (20.00%)	21 / 150 (14.00%)	2 / 11 (18.18%)
occurrences (all)	85	22	2
Dyspnoea exertional			
subjects affected / exposed	18 / 300 (6.00%)	3 / 150 (2.00%)	0 / 11 (0.00%)
occurrences (all)	22	3	0
Epistaxis			

subjects affected / exposed	26 / 300 (8.67%)	13 / 150 (8.67%)	1 / 11 (9.09%)
occurrences (all)	38	18	1
Haemoptysis			
subjects affected / exposed	0 / 300 (0.00%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	0	2	1
Productive cough			
subjects affected / exposed	5 / 300 (1.67%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	8	1	1
Psychiatric disorders			
Agitation			
subjects affected / exposed	17 / 300 (5.67%)	7 / 150 (4.67%)	0 / 11 (0.00%)
occurrences (all)	20	7	0
Anxiety			
subjects affected / exposed	15 / 300 (5.00%)	9 / 150 (6.00%)	0 / 11 (0.00%)
occurrences (all)	17	12	0
Confusional state			
subjects affected / exposed	10 / 300 (3.33%)	7 / 150 (4.67%)	1 / 11 (9.09%)
occurrences (all)	12	7	1
Delirium			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Insomnia			
subjects affected / exposed	36 / 300 (12.00%)	32 / 150 (21.33%)	0 / 11 (0.00%)
occurrences (all)	45	41	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	18 / 300 (6.00%)	6 / 150 (4.00%)	2 / 11 (18.18%)
occurrences (all)	34	9	6
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Neutrophil count decreased			
subjects affected / exposed	19 / 300 (6.33%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	92	2	2
Weight decreased			

subjects affected / exposed	15 / 300 (5.00%)	5 / 150 (3.33%)	2 / 11 (18.18%)
occurrences (all)	17	5	2
White blood cell count decreased			
subjects affected / exposed	10 / 300 (3.33%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	22	1	2
Injury, poisoning and procedural complications			
Chillblains			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	5 / 300 (1.67%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	5	3	1
Fall			
subjects affected / exposed	10 / 300 (3.33%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	11	7	5
Jaw fracture			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Post-traumatic pain			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Rib fracture			
subjects affected / exposed	7 / 300 (2.33%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	8	3	1
Skin abrasion			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	7 / 300 (2.33%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	7	4	1
Nervous system disorders			

Amnesia			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Burning sensation			
subjects affected / exposed	0 / 300 (0.00%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Carpal tunnel syndrome			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	40 / 300 (13.33%)	13 / 150 (8.67%)	0 / 11 (0.00%)
occurrences (all)	53	13	0
Headache			
subjects affected / exposed	28 / 300 (9.33%)	9 / 150 (6.00%)	1 / 11 (9.09%)
occurrences (all)	38	9	1
Lethargy			
subjects affected / exposed	9 / 300 (3.00%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	12	4	1
Neuropathy peripheral			
subjects affected / exposed	9 / 300 (3.00%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	22	2	2
Paraesthesia			
subjects affected / exposed	12 / 300 (4.00%)	6 / 150 (4.00%)	1 / 11 (9.09%)
occurrences (all)	14	6	2
Tremor			
subjects affected / exposed	19 / 300 (6.33%)	2 / 150 (1.33%)	0 / 11 (0.00%)
occurrences (all)	25	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	26 / 300 (8.67%)	4 / 150 (2.67%)	2 / 11 (18.18%)
occurrences (all)	56	10	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	159 / 300 (53.00%)	77 / 150 (51.33%)	4 / 11 (36.36%)
occurrences (all)	434	158	8
Leukopenia			

subjects affected / exposed	40 / 300 (13.33%)	8 / 150 (5.33%)	0 / 11 (0.00%)
occurrences (all)	102	29	0
Lymphopenia			
subjects affected / exposed	13 / 300 (4.33%)	8 / 150 (5.33%)	0 / 11 (0.00%)
occurrences (all)	25	13	0
Neutropenia			
subjects affected / exposed	155 / 300 (51.67%)	30 / 150 (20.00%)	5 / 11 (45.45%)
occurrences (all)	406	59	14
Thrombocytopenia			
subjects affected / exposed	87 / 300 (29.00%)	42 / 150 (28.00%)	1 / 11 (9.09%)
occurrences (all)	251	120	4
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Eye disorders			
Cataract			
subjects affected / exposed	8 / 300 (2.67%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	10	4	2
Macular pigmentation			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	8 / 300 (2.67%)	3 / 150 (2.00%)	1 / 11 (9.09%)
occurrences (all)	10	3	1
Constipation			
subjects affected / exposed	72 / 300 (24.00%)	22 / 150 (14.67%)	1 / 11 (9.09%)
occurrences (all)	108	26	1
Diarrhoea			
subjects affected / exposed	73 / 300 (24.33%)	26 / 150 (17.33%)	3 / 11 (27.27%)
occurrences (all)	123	32	4
Epigastric discomfort			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Mouth ulceration			

subjects affected / exposed	3 / 300 (1.00%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	3	2	1
Nausea			
subjects affected / exposed	57 / 300 (19.00%)	16 / 150 (10.67%)	3 / 11 (27.27%)
occurrences (all)	82	17	3
Parotid gland enlargement			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	25 / 300 (8.33%)	6 / 150 (4.00%)	1 / 11 (9.09%)
occurrences (all)	31	6	1
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Dry skin			
subjects affected / exposed	8 / 300 (2.67%)	3 / 150 (2.00%)	1 / 11 (9.09%)
occurrences (all)	8	3	1
Erythema			
subjects affected / exposed	8 / 300 (2.67%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	9	2	1
Hyperhidrosis			
subjects affected / exposed	18 / 300 (6.00%)	1 / 150 (0.67%)	0 / 11 (0.00%)
occurrences (all)	23	2	0
Hyperkeratosis			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	22 / 300 (7.33%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	26	4	1
Rash			

subjects affected / exposed	25 / 300 (8.33%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	40	1	1
Rash papular			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Swelling face			
subjects affected / exposed	2 / 300 (0.67%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	2	4	1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 300 (1.67%)	3 / 150 (2.00%)	1 / 11 (9.09%)
occurrences (all)	5	4	3
Nocturia			
subjects affected / exposed	1 / 300 (0.33%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	2 / 300 (0.67%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	2	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 300 (9.33%)	7 / 150 (4.67%)	0 / 11 (0.00%)
occurrences (all)	35	8	0
Back pain			
subjects affected / exposed	59 / 300 (19.67%)	23 / 150 (15.33%)	2 / 11 (18.18%)
occurrences (all)	69	25	4
Bone pain			
subjects affected / exposed	54 / 300 (18.00%)	20 / 150 (13.33%)	2 / 11 (18.18%)
occurrences (all)	71	27	6
Coccydynia			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	47 / 300 (15.67%)	11 / 150 (7.33%)	1 / 11 (9.09%)
occurrences (all)	68	12	3
Muscular weakness			

subjects affected / exposed	11 / 300 (3.67%)	18 / 150 (12.00%)	2 / 11 (18.18%)
occurrences (all)	17	29	3
Musculoskeletal pain			
subjects affected / exposed	18 / 300 (6.00%)	5 / 150 (3.33%)	0 / 11 (0.00%)
occurrences (all)	19	5	0
Musculoskeletal chest pain			
subjects affected / exposed	12 / 300 (4.00%)	3 / 150 (2.00%)	1 / 11 (9.09%)
occurrences (all)	14	3	1
Myalgia			
subjects affected / exposed	12 / 300 (4.00%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	14	4	1
Myopathy			
subjects affected / exposed	4 / 300 (1.33%)	11 / 150 (7.33%)	0 / 11 (0.00%)
occurrences (all)	11	24	0
Osteolysis			
subjects affected / exposed	2 / 300 (0.67%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	2	0	1
Pain in extremity			
subjects affected / exposed	21 / 300 (7.00%)	9 / 150 (6.00%)	0 / 11 (0.00%)
occurrences (all)	29	10	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	34 / 300 (11.33%)	7 / 150 (4.67%)	1 / 11 (9.09%)
occurrences (all)	51	7	1
Cellulitis			
subjects affected / exposed	6 / 300 (2.00%)	2 / 150 (1.33%)	1 / 11 (9.09%)
occurrences (all)	8	2	2
Herpes zoster			
subjects affected / exposed	6 / 300 (2.00%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	6	1	1
Nasopharyngitis			
subjects affected / exposed	30 / 300 (10.00%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	44	1	1
Pneumonia			
subjects affected / exposed	19 / 300 (6.33%)	5 / 150 (3.33%)	0 / 11 (0.00%)
occurrences (all)	20	5	0

Respiratory tract infection			
subjects affected / exposed	15 / 300 (5.00%)	5 / 150 (3.33%)	0 / 11 (0.00%)
occurrences (all)	16	5	0
Sinusitis			
subjects affected / exposed	10 / 300 (3.33%)	4 / 150 (2.67%)	1 / 11 (9.09%)
occurrences (all)	12	5	1
Tooth abscess			
subjects affected / exposed	1 / 300 (0.33%)	1 / 150 (0.67%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Upper respiratory tract infection			
subjects affected / exposed	47 / 300 (15.67%)	10 / 150 (6.67%)	2 / 11 (18.18%)
occurrences (all)	80	10	5
Urinary tract infection			
subjects affected / exposed	18 / 300 (6.00%)	6 / 150 (4.00%)	2 / 11 (18.18%)
occurrences (all)	29	9	3
Wound infection			
subjects affected / exposed	0 / 300 (0.00%)	0 / 150 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 300 (13.33%)	10 / 150 (6.67%)	3 / 11 (27.27%)
occurrences (all)	46	11	3
Dehydration			
subjects affected / exposed	14 / 300 (4.67%)	8 / 150 (5.33%)	0 / 11 (0.00%)
occurrences (all)	16	9	0
Hypercalcaemia			
subjects affected / exposed	11 / 300 (3.67%)	11 / 150 (7.33%)	0 / 11 (0.00%)
occurrences (all)	14	16	0
Hypocalcaemia			
subjects affected / exposed	14 / 300 (4.67%)	9 / 150 (6.00%)	0 / 11 (0.00%)
occurrences (all)	34	10	0
Hyperglycaemia			
subjects affected / exposed	18 / 300 (6.00%)	10 / 150 (6.67%)	0 / 11 (0.00%)
occurrences (all)	34	14	0
Hypokalaemia			

subjects affected / exposed occurrences (all)	31 / 300 (10.33%) 57	12 / 150 (8.00%) 17	0 / 11 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2010	Amendment 1 implemented the following significant changes: - The comparator treatment (Treatment Arm B) was changed from LD-dex to HD-dex. - As a direct result of the above change, the study design was changed from placebo-controlled and double-blind to active-controlled and open-label. Placebo was no longer administered in Treatment Arm B. - For the purpose of sample size calculation, the estimated median PFS was amended from 6 - 9 months to 5 - 7.5 months, to be more in agreement with median PFS seen in patients treated with HD-dex (i.e., approximately 5 months).
12 June 2011	Amendment 2 implemented the following significant changes: - Required SPMs be treated as SAEs and reported throughout the study, including LTFU, until death or 5 years after randomization, whichever occurred first. - Added Canada as a region in which the study would be conducted. - Expanded the PK sub-study from 30 subjects to all subjects who consented to sampling at select sites. - Required confirmation of investigator-assessed PD by IRAC for all subjects in both treatment arms. - Added collection of blood, bone marrow, serum, and saliva to assess the mechanism of action of pomalidomide or identify possible markers that correlate with response, including genetic aberrations. - Updated inclusion criterion to lower the eligibility requirement for measurable level of serum M-protein from 1.0 g/dL to 0.5 g/dL. - Updated exclusion criterion for serum total bilirubin to allow for higher level at study entry for subjects with hereditary enzymatic disorders such as Gilbert syndrome, glucose-6-phosphate dehydrogenase deficiency, etc. - Specified that ≥ Grade 3 rash during prior thalidomide or lenalidomide was considered hypersensitivity. - Updated language so that subjects with prior allogeneic bone marrow or allogeneic peripheral blood stem cell transplant may have been included if at least 12 months had elapsed since their transplant or if they were not on concomitant immunosuppressive mediations related to the transplant at study entry. - Allowed for collection of minimal data if available, during LTFU for subjects who discontinued the study treatment phase prior to progression. - Updated pregnancy prevention and testing requirement language to match the Pregnancy Prevention Risk Management Plan. - Updated to state only subjects randomized to Pom+LD-dex would be maintained in pregnancy pomalidomide pregnancy prevention programs.

04 November 2011	Amendment 3 implemented the following significant changes: - Added 1 site in the US - Required that exclusion criterion #2 reflect the exclusion of subjects with prior history of malignancies, other than MM, unless the subject had been free of the disease for ≥ 5 years instead of ≥ 3 years. - Updated screening requirements to reflect that, in addition to the use of growth factors, the use of platelet and/or RBC transfusions was to be allowed throughout the study, including the screening period, at the discretion of the investigator. However, subjects who failed screening as a result of neutropenia, thrombocytopenia, or anemia were not permitted to use growth factors, platelet or RBC transfusions to become eligible. - Updated to reflect that, for subjects who had a creatinine clearance less than 45 mL/min by the Cockcroft-Gault method at Screening and/or Cycle 1 Day 1, an evaluation of creatinine clearance would be performed using the 24-hour urine sample from the urine M-Protein collection. The Cockcroft-Gault method was to be used for the remainder of the study. - Clarified that after screening, a bone marrow aspirate and/or biopsy should be repeated to confirm CR and may also have been done when clinically indicated to confirm PD. - Updated inclusion criterion #8 regarding prior alkylator exposure. In addition to receiving adequate alkylator exposure as a part of SCT or minimum of 6 consecutive cycles of an alkylator based therapy, subjects may also have qualified for the study if progression on treatment with an alkylator occurred, provided that the subject received at least 2 cycles of an alkylator-containing therapy. - Updated exclusion criterion #7 to reflect that subjects who had not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment (rather than 12 months) and were currently dependent on such treatment would not be eligible for the study.
08 November 2012	- The Independent Data Monitoring Committee (IDMC) had reviewed the data related to the final PFS analysis and interim OS survival analysis. The PFS was statistically significant in favor of the pomalidomide and low-dose dexamethasone arm and the O'Brien-Fleming upper superiority boundary was crossed for overall survival. Accordingly, the IDMC recommended that subjects who were still on the high dose dexamethasone treatment should be permitted to receive pomalidomide with or without LD-dex treatment at the discretion of the Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported