Clinical trial results:
A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study To Compare The Efficacy And Safety Of Lenalidomide (Revlimid) Versus Placebo In Subjects With Transfusion-Dependent Anemia Due To Ipss Low Or Intermediate- 1 Risk Myelodysplastic Syndromes Without Deletion 5q [31] And Unresponsive Or Refractory To Erythropoiesis-Stimulating Agents

Summary

EudraCT number	2009-011513-24
Trial protocol	BE ES DE FR CZ AT IT PT GB PL
Global end of trial date	09 May 2018

Results information

Result version number	v1 (current)
This version publication date	24 May 2019
First version publication date	24 May 2019

Trial information

Trial identification

Sponsor protocol code	CC-5013-MDS-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01029262
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@celgene.com
Scientific contact	CL Beach, PharmD, Celgene Corporation, 01 913-266-0302, CLBeach@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	18 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of lenalidomide versus placebo in subjects with red blood cell (RBC) transfusion-dependent low or Int-1 risk Myelodysplastic Syndrome (MDS) associated with any karyotype except deletion 5q[31] and unresponsive or refractory to erythropoiesis- stimulating agents in the intent to treat ITT population and in the pre-specified subgroup of subjects with an erythroid differentiation signature predictive of lenalidomide response

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection; Archiving Essential Documents

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 February 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Japan: 12

Worldwide total number of subjects	239
EEA total number of subjects	185

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)	63
From 65 to 84 years	170
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 239 total sites including: Europe (185), North America (24), Asia/Pacific (13) and the Middle East (17).

Pre-assignment

Screening details:

Participants must have had transfusion-dependent anemia defined as having an average transfusion need of at least 2 units of packed red blood cells (pRBCs) per 28 days during the 112 days preceding randomization; No consecutive 56-day period that was RBC-transfusion-free during the 112 days preceding randomization; hemoglobin levels ≤ 9.5 g/dL.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received 3 placebo capsules by mouth (PO) daily (QD) for at least 168 days until disease progression occurred, intolerable side effects or withdrawal of consent.

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

Dosage and administration details:

3 placebo capsules by PO daily for at least 168 days until disease progression occurred, intolerable side effects or withdrawal of consent

Arm title	Lenalidomide

Arm description:

Participants received lenalidomide 10 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 60 mL/min for at least 168 days until disease progression, intolerable side effects or withdrawal of consent. Lenalidomide 5 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 40 and < 60 mL/min.

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

Dosage and administration details:

Lenalidomide 10 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 60 mL/min for at least 168 days until disease progression, intolerable side effects or withdrawal of consent. Lenalidomide 5 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 40 and < 60 mL/min.

Number of subjects in period 1	Placebo	Lenalidomide
Started	79	160
Completed	0	0
Not completed	79	160
Adverse event, serious fatal	-	3
Consent withdrawn by subject	10	17
Adverse event, non-fatal	9	52
Miscellaneous	1	9
Lack of therapeutic effect	57	76
Protocol deviation	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received 3 placebo capsules by mouth (PO) daily (QD) for at least 168 days until disease progression occurred, intolerable side effects or withdrawal of consent.	
Reporting group title	Lenalidomide
Reporting group description:	
Participants received lenalidomide 10 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 60 mL/min for at least 168 days until disease progression, intolerable side effects or withdrawal of consent. Lenalidomide 5 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 40 and < 60 mL/min.	

Reporting group values	Placebo	Lenalidomide	Total
Number of subjects	79	160	239
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	27	36	63
From 65-84 years	50	120	170
85 years and over	2	4	6
Age Continuous Units: years			
arithmetic mean	68.9	70.0	
standard deviation	± 8.26	± 8.19	-
Sex: Female, Male Units: Subjects			
Female	25	52	77
Male	54	108	162
Race/Ethnicity, Customized Units: Subjects			
Asian	1	1	2
Black or African American	0	2	2
White	69	133	202
Japanese	4	8	12
Other: Race Not disclosed	4	15	19
Other	1	1	2
International Prognostic Scoring System (IPSS) Investigator Determined			
The Myelodysplastic Syndrome (MDS) IPSS score assesses the severity of MDS based on 3 prognostic factors each assigned a score: the percentage of bone marrow blasts, chromosome changes in the marrow cells (karyotype) and the presence of one or more low blood cell counts (cytopenias). The IPSS score is the sum of the bone marrow blast + karyotype + cytopenia score and ranges from 0 (low risk) to 3.5 (high risk). Prognosis is categorized as Low risk (score = 0), Intermediate-1 (score 0.5 to 1.0),			

Intermediate-2 (score 1.5 to 2.0) or High risk (score ≥ 2.5).			
Units: Subjects			
Low	30	85	115
Intermediate 1	49	75	124
World Health Organization Classification 2008 of MDS by Central Review			
The World Health Organization (WHO) 2008 classification recognizes eight subtypes of MDS that are distinguished by the percentage of myeloblasts, presence or absence of ringed sideroblasts (i.e., erythroid precursors with iron deposits surrounding the nucleus), presence of a monocytosis or a deletion 5q.			
Units: Subjects			
Refractory anemia (RA)	1	1	2
Refractory cytopenia unilineage dysplasia (RCUD)	0	5	5
RA with ringed sideroblasts (RARS)	7	12	19
Refractory cytopenia multilineage dysplasia (RCMD)	59	115	174
Refractory anemia with excess blasts-1 (RAEB-1)	12	27	39
Prior Erythropoiesis-stimulating Agent (ESA) Treatment			
Erythropoiesis-stimulating agents (ESA) are similar to the cytokine (erythropoietin) that stimulates red blood cell production (erythropoieisis). ESAs, structurally and biologically, are similar to naturally occurring protein erythropoietin. ESAs are used to maintain hemoglobin at the lowest level that both minimizes transfusions and best meets a person's needs			
Units: Subjects			
Participants with Prior ESA Treatment	63	125	188
Participants with no Prior ESA Treatment	16	35	51
Gene Expression Signature			
A prespecified subgroup of participants with an erythroid differentiation gene expression signature predictive of lenalidomide response			
Units: Subjects			
Gene Expression Signature	3	14	17
No Gene Expression Signature	76	146	222
Packed RBC (pRBC) Transfusion Burden			
The baseline transfusion burden is the average number of RBC units/28 days during the 112 days prior to randomization.			
Units: pRBC units			
arithmetic mean	3.4	3.4	
standard deviation	± 1.37	± 1.23	-
Hemoglobin			
Units: g/dL			
arithmetic mean	8.7	8.7	
standard deviation	± 1.37	± 1.23	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received 3 placebo capsules by mouth (PO) daily (QD) for at least 168 days until disease progression occurred, intolerable side effects or withdrawal of consent.

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide 10 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 60 mL/min for at least 168 days until disease progression, intolerable side effects or withdrawal of consent. Lenalidomide 5 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 40 and < 60 mL/min.

Primary: Percentage of Participants Who Achieved Red Blood Cell (RBC) Transfusion Independence for ≥ 56 days as Determined by an Independent Review Committee (IRC)

End point title	Percentage of Participants Who Achieved Red Blood Cell (RBC) Transfusion Independence for ≥ 56 days as Determined by an Independent Review Committee (IRC)

End point description:

The percentage of participants who achieved the 56-day RBC transfusion independent (TI) response was defined as the absence of any RBC transfusions during any consecutive "rolling" 56-day interval within the double-blind treatment phase (ie, Days 2 (Day 1 is the first study drug day) to 57, Days 3 to 58, etcetera). The double-blind treatment phase was defined as the period between the 1st dosing up until 28 days after the last study drug dose. The ITT population includes all participants who were randomized to either lenalidomide or placebo.

End point type	Primary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: percentage of participants				
number (not applicable)	2.5	26.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	10.616
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.639
upper limit	42.702

Notes:

[1] - p-value is from Fisher's exact test to compare lenalidomide treatment group to placebo group

Primary: Percentage of Participants with a Erythroid Gene Signature Who Achieved RBC Transfusion Independence for ≥ 56 Days as Determined by an Independent Review Committee (IRC)

End point title	Percentage of Participants with a Erythroid Gene Signature Who Achieved RBC Transfusion Independence for ≥ 56 Days as Determined by an Independent Review Committee (IRC)

End point description:

The percentage of participants who achieved the 56-day RBC TI response was defined as the absence of any RBC transfusions during any consecutive "rolling" 56-day interval within the double-blind treatment phase (ie, Days 2 (Day 1 is the first study drug day) to 57, Days 3 to 58, etcetera). A participant who achieved at least a 56-day RBC-transfusion-independent response was considered a 56-day RBC-TI responder. Analysis population includes ITT participants with an erythroid gene expression signature.

End point type	Primary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	14		
Units: percentage of participants				
number (not applicable)	0.0	7.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Percentage of Participants who Achieved RBC Transfusion Independence (TI) with a Duration of ≥ 24 Weeks (168 days) as Determined by the Sponsor

End point title	Percentage of Participants who Achieved RBC Transfusion Independence (TI) with a Duration of ≥ 24 Weeks (168 days) as Determined by the Sponsor

End point description:

The 168-day RBC-transfusion-independent response was defined as the absence of any RBC transfusion during any consecutive "rolling" 168 days during the treatment period, for example Days 2 (Day 1 is the first study drug day) to 169, Days 3 to 170, Days 4 to 171, etcetera. A responder was defined as a participant who had a ≥ 168 consecutive days of RBC-transfusion-free period after the first dose of study drug in the treatment phase. The ITT population included all participants who were randomized to either lenalidomide or placebo.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: percentage of participants				
number (not applicable)	0.0	17.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001 [3]
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	99999
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99999
upper limit	99999

Notes:

[2] - 99999 = Not estimable

[3] - P-value is from Fisher's exact test to compare the lenalidomide arm to the placebo arm.

Secondary: Kaplan Meier Estimates of Duration of 56-day RBC TI response as Determined by the Sponsor

End point title	Kaplan Meier Estimates of Duration of 56-day RBC TI response as Determined by the Sponsor

End point description:

The duration of the first 56-day RBC TI response was calculated for those who achieved a response and was dependent on whether a subsequent RBC transfusion was given after the transfusion-free period (response) started:

• For those who received a subsequent RBC transfusion after the response starts, the duration of response was not censored, and was calculated as response duration = last day of response – first day of response +1 where the last day of response was defined as 1 day before the first RBC transfusion which was given at 56 days or more after the response starts.

• For those who did not receive a subsequent RBC transfusion after the response started, the end day of the response was censored and duration of response was calculated as response duration = date of last RBC transfusion assessment – first day of response + 1. Analysis included all responders who had a ≥ 56 consecutive days of RBC-transfusion-free period after the first study drug started.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[4]	41		
Units: weeks				
median (confidence interval 95%)	99999 (-99999 to 99999)	30.9 (20.7 to 59.1)		

Notes:

[4] - 99999 = Median not estimable for 1 subject

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639 [5]
Method	Logrank

Notes:

[5] - p-value from log-rank test to compare lenalidomide and placebo.

Secondary: Time to 56-Day RBC-Transfusion-independent Response as Determined by the Sponsor

End point title	Time to 56-Day RBC-Transfusion-independent Response as Determined by the Sponsor

End point description:

The time to the first 56-day RBC-transfusion-independent response was calculated for participants who achieved a response. The day from the first dose of study drug to the date at which RBC-transfusion-independence starts was achieved and calculated using: Start date of the first response period – the date of the first study drug +1. A responder was defined as a participant who had a ≥ 56 consecutive days of RBC-transfusion-free period after the first dose of study drug in the treatment phase. The analysis was conducted only for those participants who achieved a 56-day TI response according to the sponsor's assessment. Responders in the intent to treat population.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	41		
Units: weeks				
median (full range (min-max))	0.3 (0.3 to 0.3)	10.1 (0.3 to 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan Meier Estimates for Progression to Acute Myeloid Leukemia (AML)

End point title	Kaplan Meier Estimates for Progression to Acute Myeloid Leukemia (AML)

End point description:

Progression to AML is part of the natural course of MDS and is a manifestation of disease progression. The time to progress to AML was calculated from the day of randomization to the first day when AML was diagnosed. Participants who died without AML were censored at the date of death. The participants who were lost to follow-up were censored at the last known day when participants did not have AML. Participants who did not progress to AML at the last follow-up contact were censored at the day of the last follow-up contact. The ITT population included all participants who were randomized and received either lenalidomide or placebo. 99999 indicates data could not be estimated.

End point type	Secondary

End point timeframe:

From randomization to the last subject last visit date of 09 May 2018; median follow-up time for progression to AML was 2.3 years for placebo and 2.6 years for lenalidomide arm.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[6]	160[7]		
Units: years				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (5.2 to 99999)		

Notes:

[6] - 99999 = only a few subjects progressed to AML; median time to progression was not reached

[7] - 99999 = only a few subjects progressed to AML; median time to progression was not reached

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.864 [8]
Method	Logrank

Notes:

[8] - p-value from log-rank test to compare lenalidomide and placebo.

Secondary: Kaplan Meier Estimate for Overall Survival (OS)

End point title	Kaplan Meier Estimate for Overall Survival (OS)

End point description:

Overall survival was assessed using the time between randomization and the date of death or date of censoring. Participants who were alive at a data cutoff date and participants who were lost to follow-up were censored at the last date when participants were known to be alive. ITT population was all participants who were randomized. 99999 = OS could not be reached for the upper limit.

End point type	Secondary

End point timeframe:

From randomization to last subject last visit date of 09 May 2018; maximum survival follow up was 6.4 years.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[9]	160		
Units: years				
median (confidence interval 95%)	3.0 (2.3 to 99999)	3.8 (2.9 to 4.8)		

Notes:

[9] - 99999 = Placebo upper limit not estimable.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [10]
Method	Logrank

Notes:

[10] - p-value from log-rank test to compare lenalidomide and placebo.

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point description:

A TEAE = an AE that begins or worsens in intensity of frequency on or after the first dose of study drug through 28 days after last dose of study drug. A serious AE (SAE) is any:
• Death
• Life-threatening event
• Any inpatient hospitalization or prolongation of hospitalization
• Persistent or significant disability or incapacity
• Congenital anomaly or birth defect
• Any other important medical event the investigator determined the relationship of an AE to study drug based on the timing of the AE relative to drug given and whether or not other drugs, therapeutic interventions, or underlying conditions could provide an explanation for the event.
The severity of an AE was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 3.0) where Grade (GR) 1 = Mild, GR 2 = Moderate, GR 3 = Severe, GR 4 = Life-threatening and GR 5 = Death. Safety population = all patients who received ≥1 dose of lenalidomide or placebo.

End point type	Secondary

End point timeframe:

From the first dose of study drug through 28 days after discontinuation from the study treatment; up to the final data cut-off date of 03 July 2018; maximum exposure was 2100 days in the lenalidomide arm and 529 days in the placebo arm.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: participants				
At least 1 TEAE	74	160		
≥ 1 Treatment Related AE (TEAE)	42	144		
≥ 1 Treatment Related TEAE Causing Discontinuation	3	40		
≥ 1 TEAE Leading to Dose Reduction	1	10		
≥ 1 TEAE Leading to Dose Interruption	11	89		
≥ 1 TEAE Leading to Dose Interruption & Reduction	5	68		
≥ 1 TEAE Leading to Discontinuation of Study Drug	9	51		
≥ 1 Serious TEAE	16	62		
≥1 Treatment-Related Serious TEAE	3	25		
≥1 Serious TEAE Leading to Dose Reduction	0	1		
≥1 serious TEAE Leading to Dose Interruption	4	21		
≥1 SAE Causing Dose Interruption & Reduction	1	3		

≥1 Serious TEAE Leading to Stopping of Study Drug	4	24		
≥1 Grade (GR) 3-4 TEAE	35	139		
≥ 1 GR 3-4 Related TEAE	16	127		
≥ 1 GR 3-4 Leading to Dose Reduction	1	8		
≥ 1 GR 3-4 TEAE Leading to Dose Interruption	9	80		
≥ 1 GR 3-4 TEAE Dose Interrupt/Reduction	4	64		
≥ 1 GR 3-4 TEAE Leading to Stopping of Study Med	6	41		
≥ 1 GR 5 TEAE	2	6		
≥1 GR Treatment Related 5 TEAE	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Compliance Rates using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) from Baseline to Week 48

End point title	Compliance Rates using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) from Baseline to Week 48

End point description:

The EORTC QOL Questionnaire for Patients with Cancer was a 30-item oncology-specific questionnaire and was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher score on symptom scales indicating worse symptoms. A participant was considered compliant at a visit if at least 15 out of the QLQ-C30 items in the questionnaire were checked. Analyses were performed based on the Health Related Quality of Life (HRQoL) evaluable population.

End point type	Secondary

End point timeframe:

Baseline, Week 12, (±3 days), Week 24, (±3 days), Week 36, (±3 days), and Week 48 (±3 days); up to data cut-off of 17 Mar 2014

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: percentage of participants				
number (not applicable)				
Baseline	88.6	90.0		
Week 12	78.5	83.8		
Week 24	80.6	85.8		
Week 36	100.0	80.5		
Week 48	50.0	71.9		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Baseline	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.823 [11]
Method	Fisher exact

Notes:
[11] - The p-values are calculated based on the Fisher exact test.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 12 (±3 days)	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.371 [12]
Method	Fisher exact

Notes:
[12] - The p-values are calculated based on the Fisher exact test.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Week 24 (±3 days)	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.391
Method	Fisher exact

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Week 36 (±3 days)	
Comparison groups	Placebo v Lenalidomide

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Week 48 (±3 days)	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.508
Method	Fisher exact

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Fatigue Domain at Week 12 and 24

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Fatigue Domain at Week 12 and 24

End point description:

The 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 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). Analyses were performed on the HRQoL evaluable population = defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "n") are included.

End point type	Secondary

End point timeframe:

Baseline and Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 12, N = 56,122	0.6 (± 17.53)	2.4 (± 28.26)		
Week 24, N= 47, 83	7.6 (± 20.74)	-1.5 (± 26.42)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.323
Method	ANOVA

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071 [13]
Method	ANOVA

Notes:

[13] - P-value from ANOVA comparison for change from baseline between Lenalidomide and placebo adjusted with baseline score.

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Dyspnea Domain at Week 12 and 24

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Dyspnea Domain at Week 12 and 24

End point description:

The 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 Dyspnea scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate decreased dyspnea (i.e. improvement in symptom) and positive values indicate increased dyspnea (i.e. worsening of symptom). Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline and Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 12, N= 56, 122	0.6 (± 28.06)	2.2 (± 29.92)		
Week 24, N = 47, 83	4.3 (± 26.57)	1.2 (± 26.26)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76 [14]
Method	ANOVA

Notes:

[14] - P-value from ANOVA comparison for change from baseline between Lenalidomide and placebo adjusted with baseline score

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.251 [15]
Method	ANOVA

Notes:

[15] - P-value from ANOVA comparison for change from baseline between Lenalidomide and placebo adjusted with baseline score.

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain at Week 12 and 24

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Physical Functioning Domain at Week 12 and 24

End point description:

The EORTC Core Quality of Life 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 Physical Functioning Scale was scored between 0 and 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline and Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 12, N = 56,122	-1.4 (± 15.76)	-2.1 (± 18.09)		
Week 24, N= 47, 83	-5.7 (± 14.84)	-0.4 (± 18.19)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.424 [16]
Method	ANOVA

Notes:

[16] - P-value from ANOVA comparison for change from baseline between Lenalidomide and placebo adjusted with baseline score.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.116 [17]
Method	ANOVA

Notes:

[17] - P-value from ANOVA comparison for change from baseline between Lenalidomide and placebo adjusted with baseline score.

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Global Health Status/Quality of Life (QOL) Domain at Week 12 and 24

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Global Health Status/Quality of Life (QOL) Domain at Week 12 and 24

End point description:

The EORTC Core Quality of Life 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 was scored between 0 and 100, with a high score indicating better Global Health Status/QOL. Negative change from Baseline values indicate deterioration in Global Health Status/QOL and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline and Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 12, N = 56,122	-2.1 (± 20.18)	-1.4 (± 24.35)		
Week 24, N= 47, 83	-4.1 (± 20.25)	-2.4 (± 27.87)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746 [18]
Method	ANOVA

Notes:

[18] - P-value from ANOVA comparison for change from baseline between lenalidomide and placebo adjusted with baseline score.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [19]
Method	ANOVA

Notes:

[19] - P-value from ANOVA comparison for change from baseline between Lenalidomide and placebo adjusted with baseline score.

Secondary: Mean Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain at Week 12 and 24

End point title	Mean Change From Baseline in the EORTC QLQ-C30 Emotional Functioning Domain at Week 12 and 24

End point description:

The EORTC Core Quality of Life 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 Emotional Functioning Domain was scored between 0 and 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline and Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 12, N = 56,122	1.2 (± 18.70)	-1.4 (± 22.39)		
Week 24, N= 47, 83	-7.1 (± 20.78)	0.8 (± 20.06)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.265 [20]
Method	ANOVA

Notes:

[20] - P-value from ANOVA comparison for change from baseline between lenalidomide and placebo adjusted with baseline score.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [21]
Method	ANOVA

Notes:

[21] - 3]: P-value from ANOVA comparison for change from baseline between lenalidomide and placebo adjusted with baseline score.

Secondary: Mean Change from Baseline in Fatigue Domain associated with the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point title	Mean Change from Baseline in Fatigue Domain associated with the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point description:

The EORTC QLQ-C30 was a 30-item oncology-specific questionnaire. The questionnaire was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). 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). Analyses were performed on the HRQoL evaluable population.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12, N = 56,122	-0.464 (-6.562 to 5.635)	3.497 (-0.631 to 7.624)		
Week 24, N= 47, 83	7.376 (0.990 to 13.762)	0.196 (-4.505 to 4.897)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2909 [22]
Method	t-test, 2-sided

Notes:

[22] - P-value is based on a two-sample t-test comparing the difference between treatments.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:	
Week 24	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0759 [23]
Method	t-test, 2-sided

Notes:

[23] - P-value is based on a two-sample t-test comparing the difference between treatments.

Secondary: Percentage of Participants who Achieved an Erythroid Response Based on Modified International Working Group (IWG) 2006 Criteria

End point title	Percentage of Participants who Achieved an Erythroid Response Based on Modified International Working Group (IWG) 2006 Criteria

End point description:

A participant was considered as having achieved an erythroid response if they either:
- Had a hemoglobin (Hgb) increase ≥1.5 g/dL compared to baseline and confirmed by another central laboratory hemoglobin value at 4 to 8 weeks after the first Hgb measurement that also increased ≥1.5 g/dL. All Hgb values during this time interval must have had a ≥ 1.5 g/dL increase (ie, no central laboratory Hgb increase during this timeframe could be less <1.5 g/dL).

OR

- Had a 50% reduction in the number of the RBC transfusion units over any consecutive 56 days period compared to the baseline transfusion burden. The baseline transfusion burden is the number of units over 112 days prior to randomization divided by 2. Only transfusions given for a pre-transfusion Hgb value of 9 g/dL or less were used in this response assessment. Analyses = ITT population.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: percentage of participants				
number (not applicable)	30.4	38.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide

Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252 [24]
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.276
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.867
upper limit	1.877

Notes:

[24] - p-value is from Fisher's exact test to compare the lenalidomide arm to the placebo arm.

Secondary: Mean Change From Baseline in the Dyspnea Domain Associated With the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point title	Mean Change From Baseline in the Dyspnea Domain Associated With the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point description:

The 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 Dyspnea scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate decreased dyspnea (i.e. improvement in symptom) and positive values indicate increased dyspnea (i.e. worsening of symptom). Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12, N= 56, 122	1.696 (-5.313 to 8.706)	3.374 (-1.369 to 8.117)		
Week 24, N = 47, 83	5.998 (-1.174 to 13.171)	-0.206 (-5.557 to 5.146)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:	
Week 12	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6957 [25]
Method	t-test, 2-sided

Notes:

[25] - P-value is based on a two-sample t-test comparing the difference between treatments

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2
Statistical analysis description:	
Week 24	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1729 [26]
Method	t-test, 2-sided

Notes:

[26] - P-value is based on a two-sample t-test comparing the difference between treatments

Secondary: Mean Change from Baseline in the Physical Functioning Domain associated with the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point title	Mean Change from Baseline in the Physical Functioning Domain associated with the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point description:

TThe EORTC QLQ-C30 was a 30-item oncology-specific questionnaire. The questionnaire was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). The EORTC QLQ-C30 Physical Functioning was scored between 0 and 100, with a high score indicating better Global Health Status/QOL. Negative change from Baseline values indicate deterioration in Global Health Status/QOL and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population. Only subjects with available data at baseline and each time point are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12, N = 56,122	0.732 (-4.939 to 3.475)	-2.919 (-5.768 to -0.071)		

Week 24, N= 47, 83	-5.451 (-10.046 to -0.85)	-1.484 (-4.861 to 1.892)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1
Statistical analysis description: Week 12	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3975
Method	t-test, 2-sided

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2
Statistical analysis description: Week 24	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1714 [27]
Method	t-test, 2-sided

Notes:

[27] - P-value is based on a two-sample t-test comparing the difference between treatments.

Secondary: Mean Change from Baseline in the Global Health Status/QoL Domain associated with the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point title	Mean Change from Baseline in the Global Health Status/QoL Domain associated with the EORTC QLQ-C-30 Scale at Week 12 and Week 24

End point description:

The EORTC QLQ-C30 was a 30-item oncology-specific questionnaire. The questionnaire was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). The EORTC QLQ-C30 Global Health Status/QOL scale was scored between 0 and 100, with a high score indicating better Global Health Status/QOL. Negative change from Baseline values indicate deterioration in Global Health Status/QOL and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population. Only subjects with available data at baseline and each time point are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12, N = 56,122	-1.201 (-6.401 to 3.999)	-2.690 (-6.211 to 0.831)		
Week 24, N= 47, 83	-4.502 (-10.330 to 1.326)	-2.441 (-6.761 to 1.880)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6408 [28]
Method	t-test, 2-sided

Notes:

[28] - P-value is based on a two-sample t-test comparing the difference between treatments.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.575 [29]
Method	t-test, 2-sided

Notes:

[29] - P-value is based on a two-sample t-test comparing the difference between treatments.

Secondary: Mean Change From Baseline in the Emotional Functioning Domain associated with the EORTC QLQ-C30 Scale at Weeks 12 and 24

End point title	Mean Change From Baseline in the Emotional Functioning Domain associated with the EORTC QLQ-C30 Scale at Weeks 12 and 24

End point description:

The EORTC Core Quality of Life 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 Emotional Functioning Scale is scored between 0 and 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: units on a scale				
least squares mean (confidence interval 95%)				
Week 12, N = 56,122	1.458 (-3.621 to 6.536)	-1.876 (-5.307 to 1.556)		
Week 24, N= 47, 83	-6.746 (-12.228 to -1.26)	-1.129 (-5.174 to 2.917)		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2848
Method	t-test, 2-sided

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1053 [30]
Method	t-test, 1-sided

Notes:

[30] - P-value is based on a two-sample t-test comparing the difference between treatments

Secondary: Percentage of Participants with a Clinically Meaningful Improvement in QOL (EORTC QLQ-C-30 scale) from Baseline in Fatigue Domain at Weeks 12 and 24

End point title	Percentage of Participants with a Clinically Meaningful Improvement in QOL (EORTC QLQ-C-30 scale) from Baseline in Fatigue Domain at Weeks 12 and 24

End point description:

The EORTC QLQ-C30 was a 30-item oncology-specific questionnaire. The questionnaire was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher score on symptom scales indicating worse symptoms. Improvement means at least 10 points better compared to baseline. Analyses were performed on the HRQoL evaluable population. Only subjects with available data at baseline and each time point are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: percentage of participants				
number (not applicable)				
Week 12, N = 56,122	30.4	39.3		
Week 24, N= 47, 83	29.8	38.6		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042 [31]
Method	Fisher exact

Notes:

[31] - The P-values are calculated based on Fisher exact test.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.448 [32]
Method	Fisher exact

Notes:

[32] - The P-values are calculated based on Fisher exact test.

Secondary: Percentage of Participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline in the Dyspnea Domain at Weeks 12 and 24

End point title	Percentage of Participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline in the Dyspnea Domain at Weeks 12 and 24

End point description:

The EORTC Core Quality of Life 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 Dyspnea scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate decreased dyspnea (i.e. improvement in symptom) and positive values indicate increased dyspnea (i.e. worsening of symptom). Improvement means at least 10 points better compared to baseline. Analyses were performed based on the HRQoL evaluable population = all participants who completed the baseline assessment and at least one post-baseline assessment for the ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: percentage of participants				
number (not applicable)				
Week 12, N= 56, 122	19.6	21.3		
Week 24, N = 47, 83	12.8	20.5		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.825 [33]
Method	Fisher exact

Notes:

[33] - The P-values are calculated based on Fisher exact test.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568 [34]
Method	Fisher exact

Notes:

[34] - The P-values are calculated based on Fisher exact test.

Secondary: Percentage of Participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline within the Physical Functioning Domain at Weeks 12 and 24

End point title	Percentage of Participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline within the Physical Functioning Domain at Weeks 12 and 24

End point description:

The EORTC QLQ-C30 was a 30-item oncology-specific questionnaire and was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher score on symptom scales indicating worse symptoms. A change of at least 10 points on the standardized domain scores was required for it to be considered clinically meaningful. Analyses were performed on the HRQoL evaluable population. Only subjects with available data at baseline and each time point are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: percentage of participants				
number (not applicable)				
Week 12, N = 56,122	26.8	16.4		
Week 24, N= 47, 83	12.8	24.1		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1
Statistical analysis description: Week 12	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119 [35]
Method	Fisher exact

Notes:

[35] - The P-values are calculated based on Fisher exact test.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2
Statistical analysis description: Week 24	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172 [36]
Method	Fisher exact

Notes:

[36] - The P-values are calculated based on Fisher exact test.

Secondary: Percentage of participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline in the Global Health Status/QOL Domain at Weeks 12 and 24

End point title	Percentage of participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline in the Global Health Status/QOL Domain at Weeks 12 and 24

End point description:

e EORTC QLQ-C30 was a 30-item oncology-specific questionnaire and was developed to assess the quality of life of cancer patients. It contains 30 questions, 24 of which form 9 multi-item scales representing various aspects of HRQOL: 1 global scale, 5 functional scales (Physical, Role, Emotional, Cognitive and Social), and 3 symptom scales (Fatigue, Pain, and Nausea). The remaining 6 items are intended to be mono-item scales describing relevant cancer-oriented symptoms (dyspnea, insomnia, appetite, constipation, diarrhea, financial difficulties). Subscale scores are transformed to a 0 to 100 scale, with higher scores on functional scales indicating better function and higher score on symptom scales indicating worse symptoms. A change of at least 10 points on the standardized domain scores was required for it to be considered clinically meaningful. Analyses were performed on the HRQoL evaluable population. Only subjects with available data at baseline and each time point are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: percentage of participants				
number (not applicable)				
Week 12, N = 56,122	19.6	22.1		
Week 24, N= 47, 83	14.9	26.5		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1
Statistical analysis description: Week 24	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279 [37]
Method	Fisher exact

Notes:

[37] - The P-values are calculated based on Fisher exact test.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2
Statistical analysis description: Week 24	
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.792 [38]
Method	Fisher exact

Notes:

[38] - The P-values were calculated based on Fisher exact test.

Secondary: Percentage of Participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline in the Emotional Functioning Domain at Weeks 12 and 24

End point title	Percentage of Participants with a Clinically Meaningful Improvement in HRQOL Associated with the EORTC QLQ-C-30 Scale from Baseline in the Emotional Functioning Domain at Weeks 12 and 24

End point description:

The EORTC Core Quality of Life 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 Emotional Functioning Domain was scored between 0 and 100, with a high score indicating better functioning. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement. Analyses were performed on the HRQoL evaluable population, defined as all randomized subjects who completed the baseline assessment and at least one post-baseline assessment from the ITT population. Only subjects with available data at baseline and each time point (indicated by "N") are included.

End point type	Secondary

End point timeframe:

Baseline, Week 12, ±3 days and Week 24, ±3 days

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	131		
Units: percentage of participants				
number (not applicable)				
Week 12, N = 56,122	25.0	20.5		
Week 24, N= 47, 83	17.0	21.7		

Statistical analyses

Statistical analysis title	Week 12 Analysis-Statistical Analysis 1

Statistical analysis description:

Week 12

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.476 [39]
Method	Fisher exact

Notes:

[39] - The P-values are calculated based on Fisher exact test.

Statistical analysis title	Week 24 Analysis-Statistical Analysis 2

Statistical analysis description:

Week 24

Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.052 [40]
Method	Fisher exact

Notes:

[40] - The P-values are calculated based on Fisher exact test.

Secondary: Healthcare Resource Utilization (HRU): Rate of Inpatient Hospitalizations Related to Adverse Events Per Person Years

End point title	Healthcare Resource Utilization (HRU): Rate of Inpatient Hospitalizations Related to Adverse Events Per Person Years

End point description:

Hospitalizations due to adverse events exclude those for transfusions, elective procedures or protocol-driven procedures. HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient. Safety population includes all participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: Hospitilzations-person-years				
number (confidence interval 95%)	0.47 (0.3 to 0.75)	0.77 (0.62 to 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization (HRU): Duration of Hospitalizations due to Adverse Events

End point title	Healthcare Resource Utilization (HRU): Duration of Hospitalizations due to Adverse Events

End point description:

Hospitalizations due to adverse events exclude those for transfusions, elective procedures or protocol-driven procedures. HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient. Includes subjects with at least one hospitalization.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	57		
Units: Days				
median (full range (min-max))	9.0 (1.0 to 66.0)	11.0 (1.0 to 76.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization (HRU): Number of Days of Hospitalization Due to Adverse Events Per Person

End point title	Healthcare Resource Utilization (HRU): Number of Days of Hospitalization Due to Adverse Events Per Person

End point description:

Hospitalizations due to adverse events exclude those for transfusions, elective procedures or protocol-driven procedures. HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient. Safety population includes all participants who received at least 1 dose of study drug. Safety population includes all participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: Days Per Person				
number (confidence interval 95%)	6.37 (4.64 to 8.74)	8.92 (7.35 to 10.82)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Percentage of Participants who Achieved an Erythroid Response Based on Original IWG 2006 Criteria

End point title	Percentage of Participants who Achieved an Erythroid Response Based on Original IWG 2006 Criteria

End point description:

A participant was considered as having achieved an erythroid response when:
- A Hgb increase ≥1.5 g/dL compared to baseline and confirmed by another central laboratory hemoglobin value at 4 to 8 weeks after the first Hgb measurement that had also increased ≥1.5 g/dL for at least 8 weeks. All Hgb values during this time interval must have had a ≥ 1.5 g/dL increase (ie, no central laboratory Hgb increase during this timeframe can be less than a 1.5 g/dL)

OR - had an absolute reduction of 4 RBC transfusion units over any consecutive 56 days period compared to the baseline transfusion burden.

The baseline transfusion burden is the number of units over the 112 days prior to randomization divided by 2. Only transfusions given for a pre-transfusion Hgb value of 9.5 g/dL or less may be used in this response assessment.

End point type	Post-hoc

End point timeframe:

From first dose of study drug until 28 days after the last dose, as of the data cut-off date of 17 March 2014; median (minimum, maximum) duration of treatment was 168 (14, 449) and 164 (7, 1158) days in each treatment group respectively.

End point values	Placebo	Lenalidomide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	160		
Units: Percentage of Participants				
number (not applicable)	20.3	35.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Lenalidomide
Number of subjects included in analysis	239
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.017 [41]
Method	Fisher exact
Parameter estimate	Risk ratio (RR)
Point estimate	1.759
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.083
upper limit	2.856

Notes:

[41] - p-value is from Fisher's exact test to compare lenalidomide treatment group to placebo group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through 28 days after last dose; up to the final data cut-off date of 03 July 2018; maximum exposure was 2100 days in the lenalidomide treatment group and 529 days in the placebo group.

Adverse event reporting additional description:

Second primary malignancies were considered special areas of interest and were documented as a serious adverse event (considered to be at least "medically important" even if no other seriousness criteria apply) throughout the duration of this study (including the post treatment follow-up period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Lenalidomide

Reporting group description:

Participants received lenalidomide 10 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 60 mL/min for at least 168 days until disease progression, intolerable side effects or withdrawal of consent. Participants received lenalidomide 5 mg PO daily plus 2 placebo capsules for participants with a creatinine clearance ≥ 40 and < 60 mL/min.

Reporting group title	Placebo

Reporting group description:

Participants received 3 placebo capsules by mouth daily for at least 168 days until disease progression occurred, intolerable side effects or withdrawal of consent.

Serious adverse events	Lenalidomide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 160 (38.75%)	16 / 79 (20.25%)	
number of deaths (all causes)	6	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MYELODYSPLASTIC SYNDROME			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ADENOCARCINOMA OF COLON			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INVASIVE DUCTAL BREAST CARCINOMA			

subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG SQUAMOUS CELL CARCINOMA STAGE IV			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF THE TONGUE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYELOID LEUKAEMIA			
subjects affected / exposed	0 / 160 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC MYELOMONOCYTIC LEUKAEMIA			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PROSTATE CANCER			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF LUNG			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	3 / 160 (1.88%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

CIRCULATORY COLLAPSE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISUSE SYNDROME			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
PYREXIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUDDEN DEATH			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			

subjects affected / exposed	3 / 160 (1.88%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
MENTAL STATUS CHANGES			

subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FEMUR FRACTURE			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC INTRACRANIAL HAEMORRHAGE			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

CARDIAC FAILURE			
subjects affected / exposed	3 / 160 (1.88%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	2 / 160 (1.25%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 160 (0.63%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYARRHYTHMIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
ATRIAL FLUTTER			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIZZINESS			

subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSKINESIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	5 / 160 (3.13%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	3 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	3 / 160 (1.88%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOLYSIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

CATARACT			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ULCERATIVE KERATITIS			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ASCITES			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL NECROSIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INGUINAL HERNIA, OBSTRUCTIVE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

ABDOMINAL PAIN			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS NECROTISING			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATIC CIRRHOSIS			
subjects affected / exposed	1 / 160 (0.63%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN ULCER			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

NEURODERMATITIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL COLIC			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYALGIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOARTHRITIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RHABDOMYOLYSIS			

subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	10 / 160 (6.25%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	4 / 11	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
NEUTROPENIC SEPSIS			
subjects affected / exposed	3 / 160 (1.88%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATYPICAL PNEUMONIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPULMONARY ASPERGILLOSIS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CELLULITIS			
subjects affected / exposed	2 / 160 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			

subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOBAR PNEUMONIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA VIRAL			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
TOOTH ABSCESS			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	0 / 160 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	0 / 160 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAL SEPSIS			

subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 160 (0.63%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lenalidomide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 160 (96.25%)	70 / 79 (88.61%)	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	36 / 160 (22.50%)	9 / 79 (11.39%)	
occurrences (all)	49	10	
ASTHENIA			
subjects affected / exposed	38 / 160 (23.75%)	13 / 79 (16.46%)	
occurrences (all)	62	16	
OEDEMA PERIPHERAL			
subjects affected / exposed	35 / 160 (21.88%)	14 / 79 (17.72%)	
occurrences (all)	53	16	
PYREXIA			
subjects affected / exposed	20 / 160 (12.50%)	6 / 79 (7.59%)	
occurrences (all)	25	7	
Respiratory, thoracic and mediastinal disorders			
COUGH			

subjects affected / exposed	17 / 160 (10.63%)	6 / 79 (7.59%)	
occurrences (all)	21	7	
DYSPNOEA			
subjects affected / exposed	15 / 160 (9.38%)	9 / 79 (11.39%)	
occurrences (all)	19	16	
EPISTAXIS			
subjects affected / exposed	10 / 160 (6.25%)	2 / 79 (2.53%)	
occurrences (all)	12	4	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	9 / 160 (5.63%)	7 / 79 (8.86%)	
occurrences (all)	9	7	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	17 / 160 (10.63%)	2 / 79 (2.53%)	
occurrences (all)	17	2	
SERUM FERRITIN INCREASED			
subjects affected / exposed	1 / 160 (0.63%)	4 / 79 (5.06%)	
occurrences (all)	1	4	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	13 / 160 (8.13%)	2 / 79 (2.53%)	
occurrences (all)	21	3	
Injury, poisoning and procedural complications			
OVERDOSE			
subjects affected / exposed	15 / 160 (9.38%)	0 / 79 (0.00%)	
occurrences (all)	23	0	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	13 / 160 (8.13%)	9 / 79 (11.39%)	
occurrences (all)	19	11	
HEADACHE			
subjects affected / exposed	9 / 160 (5.63%)	8 / 79 (10.13%)	
occurrences (all)	15	15	
Blood and lymphatic system disorders			
NEUTROPENIA			

subjects affected / exposed	102 / 160 (63.75%)	9 / 79 (11.39%)	
occurrences (all)	323	16	
THROMBOCYTOPENIA			
subjects affected / exposed	66 / 160 (41.25%)	6 / 79 (7.59%)	
occurrences (all)	161	8	
LEUKOPENIA			
subjects affected / exposed	22 / 160 (13.75%)	2 / 79 (2.53%)	
occurrences (all)	75	2	
ANAEMIA			
subjects affected / exposed	8 / 160 (5.00%)	4 / 79 (5.06%)	
occurrences (all)	11	15	
Eye disorders			
CONJUNCTIVITIS			
subjects affected / exposed	8 / 160 (5.00%)	0 / 79 (0.00%)	
occurrences (all)	8	0	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	69 / 160 (43.13%)	18 / 79 (22.78%)	
occurrences (all)	115	27	
CONSTIPATION			
subjects affected / exposed	36 / 160 (22.50%)	9 / 79 (11.39%)	
occurrences (all)	46	9	
NAUSEA			
subjects affected / exposed	19 / 160 (11.88%)	12 / 79 (15.19%)	
occurrences (all)	29	14	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	12 / 160 (7.50%)	5 / 79 (6.33%)	
occurrences (all)	12	6	
VOMITING			
subjects affected / exposed	13 / 160 (8.13%)	5 / 79 (6.33%)	
occurrences (all)	17	5	
ABDOMINAL PAIN			
subjects affected / exposed	10 / 160 (6.25%)	5 / 79 (6.33%)	
occurrences (all)	15	6	
DYSPEPSIA			

subjects affected / exposed	8 / 160 (5.00%)	2 / 79 (2.53%)	
occurrences (all)	11	2	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	35 / 160 (21.88%)	4 / 79 (5.06%)	
occurrences (all)	61	6	
PRURITUS			
subjects affected / exposed	30 / 160 (18.75%)	9 / 79 (11.39%)	
occurrences (all)	47	13	
DRY SKIN			
subjects affected / exposed	12 / 160 (7.50%)	2 / 79 (2.53%)	
occurrences (all)	14	2	
NIGHT SWEATS			
subjects affected / exposed	8 / 160 (5.00%)	3 / 79 (3.80%)	
occurrences (all)	8	3	
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed	19 / 160 (11.88%)	2 / 79 (2.53%)	
occurrences (all)	28	3	
PAIN IN EXTREMITY			
subjects affected / exposed	18 / 160 (11.25%)	3 / 79 (3.80%)	
occurrences (all)	20	3	
BACK PAIN			
subjects affected / exposed	16 / 160 (10.00%)	9 / 79 (11.39%)	
occurrences (all)	17	9	
ARTHRALGIA			
subjects affected / exposed	14 / 160 (8.75%)	5 / 79 (6.33%)	
occurrences (all)	16	6	
MYALGIA			
subjects affected / exposed	8 / 160 (5.00%)	1 / 79 (1.27%)	
occurrences (all)	10	1	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	19 / 160 (11.88%)	9 / 79 (11.39%)	
occurrences (all)	26	11	
INFLUENZA			

subjects affected / exposed	10 / 160 (6.25%)	2 / 79 (2.53%)	
occurrences (all)	10	2	
URINARY TRACT INFECTION			
subjects affected / exposed	9 / 160 (5.63%)	6 / 79 (7.59%)	
occurrences (all)	18	6	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	4 / 160 (2.50%)	5 / 79 (6.33%)	
occurrences (all)	6	6	
PNEUMONIA			
subjects affected / exposed	4 / 160 (2.50%)	4 / 79 (5.06%)	
occurrences (all)	5	5	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	19 / 160 (11.88%)	3 / 79 (3.80%)	
occurrences (all)	22	3	
HYPOKALAEMIA			
subjects affected / exposed	10 / 160 (6.25%)	0 / 79 (0.00%)	
occurrences (all)	19	0	
IRON OVERLOAD			
subjects affected / exposed	4 / 160 (2.50%)	4 / 79 (5.06%)	
occurrences (all)	4	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2010	1. Change the CrCl exclusion criteria from < 60 mL/min to < 40 mL/min; 2. Modification of the criteria necessary to remain on treatment beyond Day 168: - The original protocol followed the IWG 2006 erythroid response criteria and required subjects to demonstrate a reduction of ≥ 4 units in 56 days prior to Day 168 in addition to a ≥ 1.5 g/dL increase in Hgb. A 50% reduction in the transfusion requirements from baseline was deemed a clinical relevant decrease with respect to the Day 168 decision point; therefore, the transfusion portion of the erythroid response requirement was modified to instead require a 50% reduction in transfusion requirement
27 April 2011	• Require that SPMs be monitored as SAEs and reported throughout the study duration including the follow-up period (at least 4 years from randomization); • Revise Dose Modification Guidelines for febrile neutropenia, Grade 4 neutropenia, Grade 3 or 4 thrombocytopenia; • Change to one Global Pregnancy Prevention Program (PPP) for all regions except Japan.
12 April 2012	• Expand exclusion criteria surrounding history of prior malignancies from 3 years to 5 years; • Revise subject eligibility criteria to exclude subjects who previously received immunomodulating or immunosuppressive agents; or epigenetic or DNA modulating agents or investigational agents; • Allow the use of anticoagulants; • Revise criteria for remaining on study drug past Day 168. Subjects need meet only one erythroid response criteria – either ≥ 1.5 g/dL Hgb increase or at least a 50% reduction in transfusion burden; rather than requiring both criteria. • Change in second primary malignancy follow-up period from at least 4 years to at least 5 years from randomization to allow for additional time to collect information.
17 September 2012	• Expand duration of enrollment period from 2 years to 3 years; • Clarify the assessments carried out by the IRC; • Clarify: the "overall population" is the "ITT population"; • Determine a new sample size (228 instead of 375); • New statistical analyses "strategy" (see Section 9.7.2).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported