

**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 \geq 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 \geq 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 | \pm 8.26 | \pm 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 | | | |
| <p>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),</p> | | | |

| | | | |
|--|------------|------------|-----|
| Intermediate-2 (score 1.5 to 2.0) or High risk (score \geq 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 (erythropoiesis). 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 | \pm 1.37 | \pm 1.23 | - |
| Hemoglobin | | | |
| Units: g/dL | | | |
| arithmetic mean | 8.7 | 8.7 | |
| standard deviation | \pm 1.37 | \pm 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 \geq 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 \geq 40 and $<$ 60 mL/min. | |

Primary: Percentage of Participants Who Achieved Red Blood Cell (RBC) Transfusion Independence for \geq 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 \geq 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 \geq 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 \geq 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 \geq 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 \geq 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 \geq 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 or 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 (\pm 20.18) | -1.4 (\pm 24.35) | | |
| Week 24, N= 47, 83 | -4.1 (\pm 20.25) | -2.4 (\pm 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 (\pm 18.70) | -1.4 (\pm 22.39) | | |
| Week 24, N = 47, 83 | -7.1 (\pm 20.78) | 0.8 (\pm 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:

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 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:

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

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

| | | | |
|--|-----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 8 / 160 (5.00%) 11 | 2 / 79 (2.53%) 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 occurrences (all) | 10 / 160 (6.25%) 10 | 2 / 79 (2.53%) 2 | |
| URINARY TRACT INFECTION subjects affected / exposed occurrences (all) | 9 / 160 (5.63%) 18 | 6 / 79 (7.59%) 6 | |
| UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) | 4 / 160 (2.50%) 6 | 5 / 79 (6.33%) 6 | |
| PNEUMONIA subjects affected / exposed occurrences (all) | 4 / 160 (2.50%) 5 | 4 / 79 (5.06%) 5 | |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE subjects affected / exposed occurrences (all) | 19 / 160 (11.88%) 22 | 3 / 79 (3.80%) 3 | |
| HYPOKALAEMIA subjects affected / exposed occurrences (all) | 10 / 160 (6.25%) 19 | 0 / 79 (0.00%) 0 | |
| IRON OVERLOAD subjects affected / exposed occurrences (all) | 4 / 160 (2.50%) 4 | 4 / 79 (5.06%) 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 clinically 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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