



Clinical trial results:

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE THE EFFICACY AND SAFETY OF ORAL AZACITIDINE PLUS BEST SUPPORTIVE CARE VERSUS PLACEBO PLUS BEST SUPPORTIVE CARE IN SUBJECTS WITH RED BLOOD CELL TRANSFUSION-DEPENDENT ANEMIA AND THROMBOCYTOPENIA DUE TO IPSS LOWER-RISK MYELODYSPLASTIC SYNDROMES

Summary

| | |
|--------------------------|--|
| EudraCT number | 2012-002471-34 |
| Trial protocol | BE NO SE ES CZ PT LT IT NL GB DE FI DK FR GR |
| Global end of trial date | 21 December 2023 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 01 January 2025 |
| First version publication date | 01 January 2025 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | AZA-MDS-003 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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 | 02 February 2024 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 December 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate RBC transfusion independence in the 2 treatment arms (oral azacitidine plus best supportive care versus placebo plus best supportive care) in subjects with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 26 April 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 18 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Canada: 11 |
| Country: Number of subjects enrolled | Czechia: 10 |
| Country: Number of subjects enrolled | Finland: 2 |
| Country: Number of subjects enrolled | France: 8 |
| Country: Number of subjects enrolled | Germany: 27 |
| Country: Number of subjects enrolled | Greece: 3 |
| Country: Number of subjects enrolled | Israel: 4 |
| Country: Number of subjects enrolled | Italy: 46 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | Mexico: 3 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Poland: 7 |
| Country: Number of subjects enrolled | Portugal: 11 |
| Country: Number of subjects enrolled | Spain: 24 |
| Country: Number of subjects enrolled | Sweden: 3 |
| Country: Number of subjects enrolled | Türkiye: 1 |
| Country: Number of subjects enrolled | United Kingdom: 18 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 12 |
| Worldwide total number of subjects | 216 |
| EEA total number of subjects | 148 |

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) | 30 |
| From 65 to 84 years | 172 |
| 85 years and over | 14 |

Subject disposition

Recruitment

Recruitment details:

Participants were randomized at 101 sites globally. The sites were located in: Europe (76), North America (13), Asia/Pacific (10), and Latin America (2). Results are reported as of the data cut-off date of 25 January 2019.

Pre-assignment

Screening details:

Participants were stratified by: average baseline (BL) Red Blood Cell (RBC) transfusion requirement (≤ 4 units versus > 4 units of RBC per 28 days), BL platelet transfusion status (dependent or independent), country of enrollment and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 to 1 versus 2).

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 | Subject, Investigator |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Oral Azacitidine Plus Best Supportive Care |

Arm description:

Participants received 300 mg oral azacitidine tablets daily (QD) on days 1 to 21 of each 28-day treatment cycle and best supportive care (BSC) which included and was not limited to packed RBC (packed red blood cell [pRBC] and whole blood), platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and granulocyte colony stimulating factors (G-CSF) for participants who experienced neutropenic fever/infections.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Azacitidine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants received 300 mg oral azacitidine tablets daily (QD) on days 1 to 21 of each 28-day treatment cycle

| | |
|------------------|-----------------------------------|
| Arm title | Placebo Plus Best Supportive Care |
|------------------|-----------------------------------|

Arm description:

Participants received identically matching placebo tablets QD on days 1 to 21 of each 28-day treatment cycle and BSC which included but was not limited to, pRBC and whole blood, platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and G-CSF for participants who experienced neutropenic fever/infections.

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

Dosage and administration details:

Participants received placebo tablets daily (QD) on days 1 to 21 of each 28-day treatment cycle

| Number of subjects in period 1 | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care |
|--------------------------------|--|--------------------------------------|
| | | |
| Started | 107 | 109 |
| Completed | 0 | 0 |
| Not completed | 107 | 109 |
| Adverse event, serious fatal | 79 | 86 |
| Consent withdrawn by subject | 13 | 12 |
| Adverse event, non-fatal | 3 | - |
| Other reasons | 11 | 8 |
| Lost to follow-up | - | 3 |
| Lack of efficacy | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | Oral Azacitidine Plus Best Supportive Care |
| Reporting group description: | |
| Participants received 300 mg oral azacitidine tablets daily (QD) on days 1 to 21 of each 28-day treatment cycle and best supportive care (BSC) which included and was not limited to packed RBC (packed red blood cell [pRBC] and whole blood), platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and granulocyte colony stimulating factors (G-CSF) for participants who experienced neutropenic fever/infections. | |
| Reporting group title | Placebo Plus Best Supportive Care |
| Reporting group description: | |
| Participants received identically matching placebo tablets QD on days 1 to 21 of each 28-day treatment cycle and BSC which included but was not limited to, pRBC and whole blood, platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and G-CSF for participants who experienced neutropenic fever/infections. | |

| Reporting group values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | Total |
|---|--|-----------------------------------|-------|
| Number of subjects | 107 | 109 | 216 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 16 | 14 | 30 |
| From 65-84 years | 85 | 87 | 172 |
| 85 years and over | 6 | 8 | 14 |
| Age Continuous Units: years | | | |
| arithmetic mean | 73.0 | 73.1 | |
| standard deviation | ± 9.23 | ± 8.36 | - |
| Sex: Female, Male Units: participants | | | |
| Female | 28 | 30 | 58 |
| Male | 79 | 79 | 158 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 96 | 99 | 195 |
| Black or African American | 1 | 0 | 1 |
| Asian | 2 | 3 | 5 |
| Native Hawaiian or Other Pacific Islanders | 0 | 0 | 0 |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Japanese | 0 | 0 | 0 |
| Other | 8 | 7 | 15 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 4 | 9 | 13 |
| Not Hispanic or Latino | 91 | 93 | 184 |
| Not Reported | 12 | 7 | 19 |
| Myelodysplastic Syndrome (MDS) World Health Organization (WHO) 2008 Classification | | | |
| The WHO 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 | | | |
| RA = Refractory Anemia | 4 | 3 | 7 |
| RN = Refractory Neutropenia | 0 | 0 | 0 |
| RT = Refractory Thrombocytopenia | 1 | 0 | 1 |
| RARS = RA with Ringed Sideroblasts | 3 | 2 | 5 |
| RCMD = R Cytopenia w/ Multilineage Dysplasia | 80 | 73 | 153 |
| RAEB-1 RA with Excess Blasts - 1 | 17 | 29 | 46 |
| RAEB-2 RA with Excess Blasts - 2 | 0 | 0 | 0 |
| MDS-U (MDS-unclassified) | 2 | 2 | 4 |
| del (5q) MDS Associated with Isolated del 5q | 0 | 0 | 0 |
| International Prognostic Scoring System (IPSS) | | | |
| The international prognostic scoring system (IPSS) is a standard for risk assessment in primary myelodysplastic syndromes (MDS) that categorizes prognoses taking into account cytogenetics, cytopenias, blasts and blood counts. The IPSS prognostic subgroups consist of low-, intermediate-1-, intermediate-2-, and high-risk groups. The scale is 0-3.5 at 0.5 increments. Scores of 0=Low; 0.5-1.0=Int-1; 1.5-2.0=Int-2; 2.5-3.5=High risk which corresponds to poorer prognosis. | | | |
| Units: Subjects | | | |
| Low | 0 | 0 | 0 |
| Intermediate 1 (0.5-1.0) | 106 | 109 | 215 |
| Intermediate 2 (1.5-2.0) | 1 | 0 | 1 |
| High | 0 | 0 | 0 |
| Platelet Transfusion Status | | | |
| Participants with thrombocytopenia were defined by 2 platelet counts that were $\leq 75 \times 10^9/\text{cells/L}$ with a platelet measurement ≥ 21 days apart. For those who were platelet transfusion-dependent at baseline and did not achieve platelet transfusion independence (TI) ≥ 56 days (8 weeks) during study treatment were considered as non-responders. For participants who were not platelet transfusion-dependent at baseline, development of platelet transfusion dependence, ie, ≥ 2 platelet transfusions in any 56-day (8 week) period during study treatment and were considered worse outcome. | | | |
| Units: Subjects | | | |
| Dependent | 30 | 35 | 65 |
| Independent | 77 | 74 | 151 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| ECOG performance status is used to describe a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale ranges from 0 to 5: 0 = Fully active, no restrictions; 1 = Restricted activity but ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out work activities; 3 = Capable to only limited self-care, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled, no self-care, confined to bed or chair; 5 = Dead. | | | |
| Units: Subjects | | | |
| Grade 0-1 | 91 | 94 | 185 |
| Grade 2 | 16 | 15 | 31 |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| Grade 5 | 0 | 0 | 0 |
| Average Red Blood Cell Transfusion Requirement (units per 28 days) | | | |
| The average red blood cell (RBC) transfusion units per 28 days is derived using transfusion records before randomization date to randomization date - 84 days (if enrolled under original protocol or protocol amendment 1), or to randomization date - 56 days (if enrolled under protocol 2). | | | |
| "99999"=N/A | | | |
| Units: units per 28 days | | | |

| | | | |
|--------------------------------|-------------|------------|---|
| median | 3.33 | 3.33 | |
| full range (min-max) | 1.3 to 10.0 | 1.3 to 9.5 | - |
| Platelet Count | | | |
| "99999"=N/A | | | |
| Units: 10 ⁹ cells/L | | | |
| arithmetic mean | 27.0 | 27.9 | |
| standard deviation | ± 15.97 | ± 18.11 | - |
| Hemoglobin | | | |
| "99999"=N/A | | | |
| Units: g/dL | | | |
| arithmetic mean | 8.22 | 8.04 | |
| standard deviation | ± 0.988 | ± 0.960 | - |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Oral Azacitidine Plus Best Supportive Care |
| Reporting group description: Participants received 300 mg oral azacitidine tablets daily (QD) on days 1 to 21 of each 28-day treatment cycle and best supportive care (BSC) which included and was not limited to packed RBC (packed red blood cell [pRBC] and whole blood), platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and granulocyte colony stimulating factors (G-CSF) for participants who experienced neutropenic fever/infections. | |
| Reporting group title | Placebo Plus Best Supportive Care |
| Reporting group description: Participants received identically matching placebo tablets QD on days 1 to 21 of each 28-day treatment cycle and BSC which included but was not limited to, pRBC and whole blood, platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and G-CSF for participants who experienced neutropenic fever/infections. | |

Primary: Percentage of Participants who Achieved Red Blood Cell (RBC) Transfusion Independence for ≥ 56 Days

| | |
|---|--|
| End point title | Percentage of Participants who Achieved Red Blood Cell (RBC) Transfusion Independence for ≥ 56 Days |
| End point description: RBC transfusion (tx) independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days within the treatment period. Participants who did not receive any RBC transfusion during a consecutive rolling 56 days (i.e., day 1 to day 56, day 2 to day 57) were considered as a 56-day RBC transfusion independent responder. | |
| End point type | Primary |
| End point timeframe: Each participant was assessed for at least 56 days or more; from the date of randomization of study drug up to the data cut-off date of 25 January 2019, approximately 5 months. | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 30.8 (22.1 to 39.6) | 11.9 (5.8 to 18.0) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | RBC Transfusion Independence for ≥ 56 Days |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |

| | |
|---|--|
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0005 ^[1] |
| Method | Stratified Mantel-Haenszel Chi-squared |
| Parameter estimate | Rate Difference |
| Point estimate | 18.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.3 |
| upper limit | 29.6 |

Notes:

[1] - 2 sided

Secondary: Duration of RBC Transfusion Independence Among Participants who Achieved RBC Transfusion Independence for at Least 56 Days

| | |
|-----------------|--|
| End point title | Duration of RBC Transfusion Independence Among Participants who Achieved RBC Transfusion Independence for at Least 56 Days |
|-----------------|--|

End point description:

Duration of RBC transfusion independence was analyzed only for participants who achieved RBC transfusion independence of ≥ 56 days on treatment. Duration of RBC transfusion independence was defined as the time from the date transfusion independence is first observed (day 1 of a ≥ 56 days period without a transfusion) until the date the participants had a subsequently documented RBC transfusion. In the event a participant had more than one ≥ 56 days rolling periods which met the RBC independence criteria, the duration with the longest rolling period was used in the analysis. Participants who maintained RBC TI through the end of the treatment period were censored at the date of treatment discontinuation, death, or 1 day before the start of the subsequent MDS treatment (if any), whichever occurred first, or the participants latest available assessment date in the database if the treatment was still on-going.

"99999"=N/A

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.1 (8.2 to 26.0) | 12.0 (2.3 to 99999) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Duration of RBC Transfusion Independence |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best |

| | |
|---|--------------------------------------|
| | Supportive Care |
| Number of subjects included in analysis | 46 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0005 |
| Method | Two-sided Unstratified Log Rank Test |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.64 |
| upper limit | 6.79 |

Secondary: Time to RBC Transfusion Independence for at Least 56 Days Among Participants who Achieved RBC Transfusion Independence for at Least 56 Days

| | |
|------------------------|--|
| End point title | Time to RBC Transfusion Independence for at Least 56 Days Among Participants who Achieved RBC Transfusion Independence for at Least 56 Days |
| End point description: | Time to RBC transfusion independence of ≥ 56 days was defined as the time between randomization and the date onset of transfusion independence was first observed (ie, Day 1 of 56 without any RBC transfusions). |
| End point type | Secondary |
| End point timeframe: | From the date of randomization of study drug up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 13 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 2.37 (0.0 to 10.9) | 2.04 (0.0 to 14.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of RBC Transfusion Reduction for Participants who Achieved RBC Transfusion Reduction of at Least 4 units of RBCs for at Least 8 Weeks

| | |
|-----------------|--|
| End point title | Duration of RBC Transfusion Reduction for Participants who Achieved RBC Transfusion Reduction of at Least 4 units of RBCs for at Least 8 Weeks |
|-----------------|--|

End point description:

A participant was considered as a RBC transfusion reduction responder if the participant had at least 4 units reduction in transfusion units over any consecutive 56 days period compared to the baseline transfusion units in 56 days.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 45 | 34 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10.0 (7.1 to 13.3) | 2.3 (2.0 to 5.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved Red Blood Cell Transfusion Independence for ≥ 84 days

| | |
|-----------------|--|
| End point title | Percentage of Participants who Achieved Red Blood Cell Transfusion Independence for ≥ 84 days |
|-----------------|--|

End point description:

RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 84 days within the treatment period. Participants who did not receive any RBC transfusion during a consecutive rolling 84 days (i.e., day 1 to day 84, day 2 to day 85) were considered as a 84-day RBC transfusion independent responder.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 28.0 (19.5 to 36.5) | 6.4 (1.8 to 11.0) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | RBC Transfusion Independence for ≥ 84 days |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.0001 [2] |
| Method | Stratified Mantel-Haenszel; Chi-squared |
| Parameter estimate | Rate Difference |
| Point estimate | 21.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.9 |
| upper limit | 31.3 |

Notes:

[2] - 2 sided

Secondary: Duration of RBC Transfusion Independence Among Participants who Achieved RBC Transfusion Independence for at Least 84 Days

| | |
|-----------------|--|
| End point title | Duration of RBC Transfusion Independence Among Participants who Achieved RBC Transfusion Independence for at Least 84 Days |
|-----------------|--|

End point description:

Duration of RBC transfusion independence was analyzed only for participants who achieved RBC transfusion independence of ≥ 84 days on treatment. Duration of RBC transfusion independence was defined as the time from the date transfusion independence is first observed (day 1 of a ≥ 84 days period without a transfusion) until the date the participants had a subsequently documented RBC transfusion. In case a participant had more than one ≥ 84 days rolling periods which met the RBC independence criteria, the duration with the longest rolling period was used in the analysis.

"99999"=N/A

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 7 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.1 (8.2 to 26.0) | 99999 (5.0 to 99999) | | |

Statistical analyses

| Statistical analysis title | Duration of RBC Transfusion Independence |
|---|--|
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.4347 |
| Method | Two-Sided Unstratified Log Rank Test |

Secondary: Time to RBC Transfusion Independence for at Least 84 Days Among Participants who Achieved RBC Transfusion Independence for at Least 84 Days

| | |
|-----------------|---|
| End point title | Time to RBC Transfusion Independence for at Least 84 Days Among Participants who Achieved RBC Transfusion Independence for at Least 84 Days |
|-----------------|---|

End point description:

Time to RBC transfusion independence of ≥ 84 days was defined as the time between randomization and the date onset of transfusion independence was first observed (i.e., Day 1 of 84 without any RBC transfusions).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 7 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 2.64 (0.0 to 9.9) | 4.01 (0.5 to 14.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Erythroid Hematological Improvement (HI-E) Response According to 2006 IWG Criteria

| | |
|-----------------|---|
| End point title | Percentage of Participants with an Erythroid Hematological Improvement (HI-E) Response According to 2006 IWG Criteria |
|-----------------|---|

End point description:

Erythroid HI-E improvement was defined as a hemoglobin increase of ≥ 1.5 g/dL; or a reduction in units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a hemoglobin of ≤ 9.0 g/dL on treatment were counted in the RBC transfusion response evaluation.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | | | | |
| HI-E Response | 43.0 (33.6 to 52.4) | 32.1 (23.3 to 40.9) | | |
| ≥ 1.5 g/dL Hemoglobin Increase | 23.4 (15.3 to 31.4) | 5.5 (1.2 to 9.8) | | |
| RBC Transfusion Reduction | 42.1 (32.7 to 51.4) | 31.2 (22.5 to 39.9) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Erythroid Hematological Improvement (HI-E) |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1467 |
| Method | Stratified Mantel-Haenszel. Chi-squared |
| Parameter estimate | Rate Difference |
| Point estimate | 10.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 23.7 |

| | |
|---|--|
| Statistical analysis title | Erythroid Hematological Improvement (HI-E) |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.1431 |
| Method | Stratified Mantel-Haenszel. Chi-squared |
| Parameter estimate | Rate Difference |
| Point estimate | 10.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9 |
| upper limit | 23.6 |

| | |
|---|--|
| Statistical analysis title | Erythroid Hematological Improvement (HI-E) |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0002 |
| Method | Stratified Mantel-Haenszel. Chi-squared |
| Parameter estimate | Rate Difference |
| Point estimate | 17.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 8.8 |
| upper limit | 26.9 |

Secondary: Percentage of Participants with a Hematological Improvement Response in Platelets (HI-P) According to 2006 IWG Criteria

| | |
|--|---|
| End point title | Percentage of Participants with a Hematological Improvement Response in Platelets (HI-P) According to 2006 IWG Criteria |
| End point description: | |
| HI-P response was defined according to IWG 2006 criteria (Cheson, 2006) and as: 1. Absolute increase of $\geq 30 \times 10^9/L$ for participants starting with $> 20 \times 10^9/L$ platelets; 2. Increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by at least 100%. HI-P must have lasted at least 8 weeks. | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 24.3 (16.2 to 32.4) | 7.3 (2.4 to 12.2) | | |

Statistical analyses

| Statistical analysis title | HI-P |
|---|--|
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0007 |
| Method | Stratified Mantel-Haenszel. Chi-squared |
| Parameter estimate | Rate Difference |
| Point estimate | 17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 7.5 |
| upper limit | 26.4 |

Secondary: Percentage of Participants who Achieved Platelet Transfusion Independence with a Duration of ≥ 8 weeks (56 days)

| | |
|------------------------|---|
| End point title | Percentage of Participants who Achieved Platelet Transfusion Independence with a Duration of ≥ 8 weeks (56 days) |
| End point description: | <p>Platelet transfusion independence was defined as the absence of any platelet transfusion during any consecutive "rolling" 56 days during the treatment period, (ie, Day 1 to 56, Day 2 to 57, Days 3 to 58, etc.). Participants were considered platelet transfusion dependent at baseline if they had received ≥ 2 platelet transfusions during the 56 days immediately preceding randomization and had no consecutive 28-day period during which no platelet transfusions were administered.</p> |
| End point type | Secondary |
| End point timeframe: | <p>From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo</p> |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 35 | | |
| Units: Percentage Participants | | | | |
| number (not applicable) | 16.7 | 14.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Platelet Transfusion Independence

| | |
|-----------------|---|
| End point title | Time to Platelet Transfusion Independence |
|-----------------|---|

End point description:

Time to platelet transfusion independence was defined as the time between randomization and the first documented date of onset of transfusion independence (ie, Day 1 of 56 without any platelet transfusions).

"99999"=N/A

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the date of randomization of study drug up to the treatment period; up to the data cut-off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5 | 5 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 9.6 (9.6 to 10.9) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

Overall survival was defined as the time from randomization to death from any cause and was calculated using randomization date and date of death, or date of last follow-up for censored participants. All subjects were followed until drop out (withdrawal of consent from further data collection or lost to follow-up), death, or study closure. Participants who dropped out or were alive at study closure (or at the time of the interim analysis) had their OS times censored at the time of last contact, as appropriate.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomization up to death from any cause; up to a maximum of approximately 10 years on study; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 17.3 (12.9 to 20.8) | 16.7 (12.8 to 24.0) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | OS |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 216 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.6257 |
| Method | Logrank |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.49 |

Secondary: Percentage of Participants with a Hematologic Response According to the 2006 IWG Criteria for MDS

| | |
|--|---|
| End point title | Percentage of Participants with a Hematologic Response According to the 2006 IWG Criteria for MDS |
| End point description: | |
| Hematologic response was defined as: • A complete response (CR): <5% myeloblasts, and normal maturation of all cell lines; Peripheral blood (PB) shows: hemoglobin >10 g/dL, neutrophils $\geq 1.0 \times 10^9/L$, platelets $\geq 100 \times 10^9/dL$, blasts (0%) • Partial Response (PR): same as CR bone marrow (BM) shows blasts decreased by $\geq 50\%$ over pre-treatment but still > 5%; Cellularity and morphology not relevant • Marrow CR: BM: $\leq 5\%$ myeloblasts and decrease by $\geq 50\%$ over pre-treatment PB • Stable disease (SD): failure to achieve at least PR, but no evidence of progression for > 8 wks • Failure: death during treatment or disease progression • Disease Progression for those with: - Less than 5% blasts: $\geq 50\%$ increase in blasts to > 5% blasts - 5%-10% blasts: $\geq 50\%$ increase to > 10% blasts - 10%-20% blasts: $\geq 50\%$ increase to > 20% blasts - 20%-30% blasts $\geq 50\%$ increase to > 30% blasts Any of the following: - $\geq 50\%$ decrease from maximum remission/response in granulocytes or platelets | |
| End point type | Secondary |

End point timeframe:

Response was assessed every 3 cycles; up to the data cut-off date of 25 Jan 2019; median duration of exposure to oral azacitidine was 86.0 days and 119.0 days for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Complete Response (CR) | 7.7 | 0 | | |
| Partial Response | 0 | 0 | | |
| Marrow CR | 23.1 | 4.2 | | |
| Stable Disease (SD) | 2.8 | 30.3 | | |
| Disease Progression | 62.6 | 46.8 | | |
| Failure due to Death | 0.9 | 0.9 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Progressed to Acute Myeloid Leukemia (AML)

| | |
|------------------------|--|
| End point title | Percentage of Participants who Progressed to Acute Myeloid Leukemia (AML) |
| End point description: | Participants with a documented diagnosis of AML arising from previous MDS documented diagnosis. |
| End point type | Secondary |
| End point timeframe: | From randomization of study drug to the end up to final data cut-off date of 25 January 2019; maximum follow-up time was 67.9 months for azacitidine and 64.8 months for placebo group |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 7.5 | 16.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression to Acute Myeloid Leukemia (AML) Among Participants who Progressed to AML

| | |
|-----------------|--|
| End point title | Time to Progression to Acute Myeloid Leukemia (AML) Among Participants who Progressed to AML |
|-----------------|--|

End point description:

Time to AML progression was defined as the time from the date of randomization until the date the subject has documented progression to AML. For participants who had progression to AML documented in MLL central lab report, the earliest sample collection date with the diagnosis of "s-AML arising from previous MDS" was used as the date to AML progression.

"99999"=N/A

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization of study drug to progression of AML; up to a maximum of approximately 10 years on study; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 18 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 99999 (99999 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Significant Bleeding Events

| | |
|-----------------|---|
| End point title | Percentage of Participants with Significant Bleeding Events |
|-----------------|---|

End point description:

Clinically significant bleeding event was defined as: any intracranial or retroperitoneal bleed; bleeding requiring transfusions of > 2 units of blood/blood products; bleeding associated with a decrease in hemoglobin of > 2 g/dL; or bleeding from any site requiring transfusions of > 2 units of blood.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization until 28 days after the last dose of IP; up to data cut off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 8.4 | 9.2 | | |

Statistical analyses

No statistical analyses for this end point

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 was defined as an adverse event that begins or worsens in intensity of frequency on or after the first dose of study drug through 28 days after last dose of study drug. A serious adverse event (SAE) is any: • Death; • Life-threatening event; • Any inpatient hospitalization or prolongation of existing 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 administration and whether or not other drugs, therapeutic interventions, or underlying conditions could provide a sufficient explanation for the event. The severity of an AE was evaluated by the investigator according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.0) where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening and Grade 5 = Death. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose of IP up to 28 days after the last dose of IP; up to a maximum of approximately 10 years on study; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|---|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Participants | | | | |
| ≥ 1 TEAE | 107 | 108 | | |
| ≥ 1 TEAE Related to Study Drug | 102 | 54 | | |
| ≥ 1 Serious TEAE | 83 | 69 | | |
| ≥ 1 Serious TEAE Related to Study Drug | 38 | 8 | | |
| ≥ 1 Grade (GR) 3-4 TEAE | 98 | 81 | | |
| ≥ 1 Grade 3-4 TEAE Related to Study Drug | 73 | 20 | | |
| ≥ 1 Grade (GR) 3-4 Serious TEAE | 79 | 56 | | |
| ≥ 1 GR 3-4 Serious TEAE Related to Study Drug | 38 | 5 | | |
| ≥ 1 TEAE Leading to Death | 25 | 14 | | |

| | | | | |
|---|----|----|--|--|
| ≥ 1 TEAE Related to Study Drug Leading to Death | 9 | 2 | | |
| ≥ 1 TEAE Leading to Dose Reduction | 31 | 4 | | |
| ≥ 1 TEAE Leading to Dose Interruption | 68 | 40 | | |
| ≥ 1 TEAE Leading to Dose Interruption/Reduction | 29 | 2 | | |
| ≥ 1 TEAE Leading to Treatment Discontinuation | 34 | 31 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in the Physical Well-Being Component of the Functional Assessment of Cancer Therapy-Anemia (FACT-An) Endpoints at Cycle 6

| | |
|-----------------|---|
| End point title | Mean Change From Baseline in the Physical Well-Being Component of the Functional Assessment of Cancer Therapy-Anemia (FACT-An) Endpoints at Cycle 6 |
|-----------------|---|

End point description:

The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being (PWG), social/family (SWB), emotional well being (EWB) and Functional Well-Being (FWB) and an additional 20-item anemia questionnaire that measures fatigue associated items and 7 non-fatigue items. The scales are formatted on 1 to 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general health related quality of life (HRQoL), the FACT-An measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various therapeutic areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest QOL and 100 denotes the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 0.2 (± 4.12) | -0.8 (± 3.91) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | FACT-An |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |

| | |
|---|-----------------|
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.214 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Social Well-Being Component of the Functional Assessment of Cancer Therapy-Anemia Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Mean Change From Baseline in the Social Well-Being Component of the Functional Assessment of Cancer Therapy-Anemia Instrument at Cycle 6 |
|-----------------|--|

End point description:

The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being (PWG), social/family (SWB), emotional well being (EWB) and Functional Well-Being (FWB) and an additional 20-item anemia questionnaire that measures fatigue associated items and 7 non-fatigue items. The scales are formatted on 1 to 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general health related quality of life (HRQoL), the FACT-An measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various therapeutic areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest QOL and 100 denotes the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | -0.4 (± 3.96) | -1.1 (± 4.69) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Social Well-Being |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.446 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Emotional Well-Being Component of the Functional Assessment of Cancer Therapy-Anemia Instrument at Cycle 6

| | |
|---|---|
| End point title | Mean Change From Baseline in the Emotional Well-Being Component of the Functional Assessment of Cancer Therapy-Anemia Instrument at Cycle 6 |
| End point description: The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being (PWG), social/family (SWB), emotional well being (EWB) and Functional Well-Being (FWB) and an additional 20-item anemia questionnaire that measures fatigue associated items and 7 non-fatigue items. The scales are formatted on 1 to 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general health related quality of life (HRQoL), the FACT-An measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various therapeutic areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest QOL and 100 denotes the highest QOL. | |
| End point type | Secondary |
| End point timeframe: Baseline to Cycle 6 Day 1 | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 1.3 (± 4.33) | 0.2 (± 4.35) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Emotional Well-Being |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.248 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Functional Well-Being Component of the FACT-An Instrument at Cycle 6

| | |
|---|---|
| End point title | Mean Change From Baseline in the Functional Well-Being Component of the FACT-An Instrument at Cycle 6 |
| End point description: The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being (PWG), social/family (SWB), emotional well being (EWB) and Functional Well-Being (FWB) and an additional 20-item anemia questionnaire that measures fatigue associated items and 7 non-fatigue items. The scales are formatted on 1 to 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = | |

Quite a Bit and 4 = Very much). Also, general health related quality of life (HRQoL), the FACT-An measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various therapeutic areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest QOL and 100 denotes the highest QOL.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Cycle 6 Day 1 | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 0.5 (± 3.95) | -1.2 (± 4.45) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Functional Well-Being |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.058 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Anemia Subscale within FACT-An Instrument at Cycle 6

| | |
|-----------------|---|
| End point title | Mean Change From Baseline in the Anemia Subscale within FACT-An Instrument at Cycle 6 |
|-----------------|---|

End point description:

The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being (PWG), social/family (SWB), emotional well being (EWB) and Functional Well-Being (FWB) and an additional 20-item anemia questionnaire that measures fatigue associated items and 7 non-fatigue items. The scales are formatted on 1 to 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general health related quality of life (HRQoL), the FACT-An measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various therapeutic areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest QOL and 100 denotes the highest QOL.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Cycle 6 Day 1 | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 2.9 (± 11.81) | -0.6 (± 10.39) | | |

Statistical analyses

| Statistical analysis title | Anemia |
|---|--|
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.13 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Fatigue-Related Subscale within the FACT-An Instrument at Cycle 6

| | |
|--|--|
| End point title | Mean Change From Baseline in the Fatigue-Related Subscale within the FACT-An Instrument at Cycle 6 |
| End point description: | |
| <p>The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being (PWG), social/family (SWB), emotional well being (EWB) and Functional Well-Being (FWB) and an additional 20-item anemia questionnaire that measures fatigue associated items and 7 non-fatigue items. The scales are formatted on 1 to 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general health related quality of life (HRQoL), the FACT-An measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various therapeutic areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest QOL and 100 denotes the highest QOL.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Cycle 6 Day 1 | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 2.1 (\pm 8.74) | -0.6 (\pm 7.84) | | |

Statistical analyses

| Statistical analysis title | Fatigue |
|---|--|
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.123 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Functional Assessment of Cancer Therapy-Anemia Trial Outcome Index (FACT-An TOI) Summary Scale within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Mean Change From Baseline in the Functional Assessment of Cancer Therapy-Anemia Trial Outcome Index (FACT-An TOI) Summary Scale within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

The FACT-G and FACT-An score are summed to form the FACT-An total score. The FACT-An Trial Outcome Index (TOI) consists of the summation of a "summary scale" and includes the Physical Well-being, (PWB; 7 items; score range, 0–28), the Functional Well-being (7 items; score range, 0–28) and the Anemia subscale consisting of 20 items on the same five-point scale, with 13 of them measuring fatigue related symptoms (FS) and seven measuring non-FS. The FACT-An TOI has been demonstrated to be a sensitive indicator of clinical outcomes in a number of diseases including MDS. The Fact-TOI score ranges from 0 to 136. Higher scores on all scales of the Fact-An and subscales on the FACT-TOI reflect better quality of life or fewer symptoms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 3.7 (\pm 17.29) | -2.7 (\pm 15.45) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | FACT-An TOI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.069 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Functional Assessment of Cancer Therapy-Anemia-General (FACT-G) Summary Scale within the FACT-An Instrument at Cycle 6

| | |
|-----------------|---|
| End point title | Mean Change From Baseline in the Functional Assessment of Cancer Therapy-Anemia-General (FACT-G) Summary Scale within the FACT-An Instrument at Cycle 6 |
|-----------------|---|

End point description:

The FACT-An is a 47-item, cancer-specific questionnaire consisting of a core 27-item general questionnaire (i.e., the Functional Assessment of Cancer Therapy-General [FACT-G]). The FACT-G measures the 4 domains on a 5-point scale ranging from 0 (not at all) to 4 (very much). The 4 domains are: • Physical Well-being (PWB; 7 items; score range, 0–28), • Social/Family Well-being (SWB; 7 items; score range, 0–28), • Emotional Well-being (EWB; 6 items; score range, 0–24), and • Functional Well-being (7 items; score range, 0–28). The FACT-G is a summation composed of a "summary scale" including the PWB, SWB, EWB and FWB. The FACT-G score range is from 0 to 108. For all summary scales including FACT-G, a higher score indicates better HRQoL or lower level of symptoms.

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Cycle 6 Day 1 | |

| | | | | |
|--------------------------------------|--|-----------------------------------|--|--|
| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 1.6 (± 12.00) | -2.9 (± 12.11) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | FACT-G |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.078 |
| Method | t-test, 2-sided |

Secondary: Mean Change From Baseline in the Functional Assessment of Cancer Therapy-Anemia-Total Score at Cycle 6

| | |
|-----------------|--|
| End point title | Mean Change From Baseline in the Functional Assessment of Cancer Therapy-Anemia-Total Score at Cycle 6 |
|-----------------|--|

End point description:

The FACT-G and the anemia subscale (AnS) are summed to form the FACT-An total score and the total score ranges from 0 to 188. The FACT-G measures the 4 domains on a 5-point scale ranging from 0 (not at all) to 4 (very much). The 4 domains are: • Physical Well-being (PWB; 7 items; score range, 0–28), • Social/Family Well-being (SWB; 7 items; score range, 0–28), • Emotional Well-being (EWB; 6 items; score range, 0–24), and • Functional Well-being (7 items; score range, 0–28). The AnS consists of 20 items on the same 5-point scale, with 13 of them measuring fatigue-related symptoms (FS) and 7 measuring non-FS. The AnS and FS scores can range from 0–80 and 0–52, respectively. For all domains and summary subscales, a higher score indicates better HRQoL or lower level of symptoms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|--------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 42 | 49 | | |
| Units: Units on a Scale | | | | |
| arithmetic mean (standard deviation) | 4.5 (± 21.88) | -3.5 (± 20.62) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Anemia Total Score |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 91 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.073 |
| Method | t-test, 2-sided |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Physical Well-Being Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Physical Well-Being Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 17.3 | 13.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.56 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.3 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Social Well-Being Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Social Well-Being Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 11.1 | 14.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Social Well-Being |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.48 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 1.78 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Emotional Well-Being Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|---|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Emotional Well-Being Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|---|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 23.5 | 15.8 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.197 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 1.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 3.65 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Functional Well-Being Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Functional Well-Being Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 14.8 | 8.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.121 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 2.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 5.57 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Anemia Subscale Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline on the Anemia Subscale Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 27.2 | 15.8 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.075 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 4.3 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Fatigue Related Symptoms Subscale Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Fatigue Related Symptoms Subscale Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 27.2 | 18.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.222 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 1.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 3.29 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Functional Assessment of Cancer Therapy-Anemia Trial Outcome Index Subscale Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Functional Assessment of Cancer Therapy-Anemia Trial Outcome Index Subscale Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 19.8 | 12.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.249 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 3.83 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Functional Assessment of Cancer Therapy-Anemia-General Subscale Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Functional Assessment of Cancer Therapy-Anemia-General Subscale Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|--|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 23.5 | 13.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.082 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 2.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.92 |
| upper limit | 4.48 |

Secondary: Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Functional Assessment of Cancer Therapy Anemia-Total Score Domain within the FACT-An Instrument at Cycle 6

| | |
|-----------------|---|
| End point title | Percentage of Participants with a Clinically Meaningful Improvement (CMI) From Baseline in the Functional Assessment of Cancer Therapy Anemia-Total Score Domain within the FACT-An Instrument at Cycle 6 |
|-----------------|---|

End point description:

A clinically meaningful improvement or deterioration was defined by domain specific thresholds of change from baseline. The FACT-An questionnaire is a 47-item, cancer specific questionnaire consisting of a core 27 items measuring 4 general domains physical well being, social/family, emotional well being and Functional Well-Being and an additional 20-item anemia questionnaire that measures fatigue and 7 non-fatigue items. The scales are formatted on 4 pages for self-administration using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a Bit and 4 = Very much). Also, general HRQoL measures the impact of fatigue and other anemia-related symptoms on patient functioning and is used to assess the effect of treatments in various areas, including MDS. The instrument and the fatigue and non-fatigue subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 = the poorest QOL and 100 = the highest QOL.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | 19.8 | 11.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CMI |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.153 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Common Odds Ratio |
| Point estimate | 1.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 4.34 |

Secondary: Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 2 Day 1 (C2D1)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 2 Day 1 (C2D1) |
|-----------------|---|

End point description:

The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 2 Day 1 (C2D1)

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 2.5 | 10.5 | | |
| No Change | 30.9 | 49.5 | | |
| Worsened by 1 Level | 25.9 | 23.2 | | |
| Worsened by 2 Levels | 23.5 | 6.3 | | |
| Missing | 17.3 | 10.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | < 0.001 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Change from Baseline in Responses to

the Fact-Anemia Item GP-5 - Cycle 3 Day 1 (C3D1)

| | |
|---|---|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 3 Day 1 (C3D1) |
| End point description: The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Cycle 3 Day 1 (C3D1) | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| No Change | 24.7 | 41.1 | | |
| Worsened by 1 Level | 16.0 | 18.9 | | |
| Worsened by 2 Levels | 23.5 | 13.7 | | |
| Missing | 28.4 | 15.8 | | |
| Improved | 7.4 | 10.5 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Responses to the Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.046 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 4 Day 1 (C4D1)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 4 Day 1 (C4D1) |
|-----------------|---|

End point description:

The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group.

| | |
|---------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Cycle 4 Day 1 (C4D1) | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 2.5 | 9.5 | | |
| No Change | 32.1 | 37.9 | | |
| Worsened by 1 Level | 16.0 | 14.7 | | |
| Worsened by 2 Levels | 14.8 | 6.3 | | |
| Missing | 34.6 | 31.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.134 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 5 Day 1 (C5D1)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 5 Day 1 (C5D1) |
|-----------------|---|

End point description:

The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of

change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥ 2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group.

| | |
|---------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline to Cycle 5 Day 1 (C5D1) | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 2.5 | 7.4 | | |
| No Change | 25.9 | 34.7 | | |
| Worsened by 1 Level | 13.6 | 12.6 | | |
| Worsened by 2 Levels | 8.6 | 5.3 | | |
| Missing | 49.4 | 40.0 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.324 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 6 Day 1 (C6 D1)

| | |
|-----------------|--|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 6 Day 1 (C6 D1) |
|-----------------|--|

End point description:

The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥ 2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 6 Day 1 (C6 D1)

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 1.2 | 4.2 | | |
| No Change | 25.9 | 27.4 | | |
| Worsened by 1 Level | 9.9 | 12.6 | | |
| Worsened by 2 Levels | 14.8 | 7.4 | | |
| Missing | 48.1 | 48.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.442 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 7 Day 1 (C7D1)

| | |
|-----------------|---|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - Cycle 7 Day 1 (C7D1) |
|-----------------|---|

End point description:

The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 7 Day 1 (C7D1)

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 1.2 | 1.1 | | |
| No Change | 25.9 | 21.1 | | |
| Worsened by 1 Level | 11.1 | 3.2 | | |
| Worsened by 2 Levels | 7.4 | 3.2 | | |
| Missing | 54.3 | 71.6 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.063 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - End of Treatment

| | |
|---|---|
| End point title | Percentage of Participants with Change from Baseline in Responses to the Fact-Anemia Item GP-5 - End of Treatment |
| End point description: The distribution (frequency and percentage) of the observed responses (i.e., "Not at all (0)," "A little bit (1)," "Somewhat (2)," "Quite a bit (3)," "Very much (4)," and missing) to Item GP-5 ("I am bothered by side effects of treatment" in the past seven days) of the FACT-An at each scheduled visit were summarized for each treatment group. The denominator for the percentage calculation per treatment group was based on the number of the FACT-An evaluable population at baseline. The distribution of change in responses (improved [i.e., change score from 1 to 4], no change [0], worsened by one level [-1], worsened by ≥2 levels [-2 to -4], and missing) from baseline at each post-baseline scheduled visit were summarized by treatment group. | |
| End point type | Secondary |
| End point timeframe: From Baseline to End of Treatment | |

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 2.5 | 6.3 | | |
| No Change | 14.8 | 25.3 | | |
| Worsened by 1 Level | 9.9 | 8.4 | | |
| Worsened by 2 Levels | 9.9 | 12.6 | | |
| Missing | 63.0 | 47.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Fact-Anemia Item GP-5 |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.198 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level (EQ-5D-3L) Mobility Dimension Responses at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level (EQ-5D-3L) Mobility Dimension Responses at Cycle 6 |
|-----------------|--|

End point description:

The EQ-5D-3L is a generic, self-administered questionnaire that consists of 5 dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has 3 levels of severity corresponding to no problems, some problems, and extreme problems. It also includes a Visual Analog Scale that recorded the respondent's self-rated health on a vertical, 0–100 scale, where 100 = Best imaginable health state and 0 = Worst imaginable health state. Distribution of the observed responses (i.e., no problems, moderate problems, severe problems, and missing) of the 5 dimensions at each visit was summarized per arm. The denominator for the percentage calculation per group was based on the number of the EQ-5D-3L evaluable population at baseline. The distribution of change in responses (i.e., improved [by ≥1 level], no change, worsened [by ≥1 level], and missing) from baseline are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 8.6 | 8.4 | | |
| No Change | 35.8 | 33.7 | | |
| Worsened | 7.4 | 9.5 | | |
| Missing | 48.1 | 48.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ-5D-3L |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.972 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level of Self-Care Dimension Responses at Cycle 6

| | |
|-----------------|---|
| End point title | Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level of Self-Care Dimension Responses at Cycle 6 |
|-----------------|---|

End point description:

The EQ-5D-3L is a generic, self-administered questionnaire that consists of 5 dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has 3 levels of severity corresponding to no problems, some problems, and extreme problems. It also includes a Visual Analog Scale that recorded the respondent's self-rated health on a vertical, 0–100 scale, where 100 = Best imaginable health state and 0 = Worst imaginable health state. Distribution of the observed responses (i.e., no problems, moderate problems, severe problems, and missing) of the 5 dimensions at each visit was summarized per arm. The denominator for the percentage calculation per group was based on the number of the EQ-5D-3L evaluable population at baseline. The distribution of change in responses (i.e., improved [by ≥1 level], no change, worsened [by ≥1 level], and missing) from baseline are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 2.5 | 4.2 | | |
| No Change | 42.0 | 44.2 | | |
| Worsened | 7.4 | 3.2 | | |
| Missing | 48.1 | 48.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | European Quality of Life |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.601 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level Usual Activities Dimension Responses at Cycle 6

| | |
|-----------------|---|
| End point title | Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level Usual Activities Dimension Responses at Cycle 6 |
|-----------------|---|

End point description:

The EQ-5D-3L is a generic, self-administered questionnaire that consists of 5 dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has 3 levels of severity corresponding to no problems, some problems, and extreme problems. It also includes a Visual Analog Scale that recorded the respondent's self-rated health on a vertical, 0–100 scale, where 100 = Best imaginable health state and 0 = Worst imaginable health state. Distribution of the observed responses (i.e., no problems, moderate problems, severe problems, and missing) of the 5 dimensions at each visit was summarized per arm. The denominator for the percentage calculation per group was based on the number of the EQ-5D-3L evaluable population at baseline. The distribution of change in responses (i.e., improved [by ≥1 level], no change, worsened [by ≥1 level], and missing) from baseline are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 11.1 | 3.2 | | |
| No Change | 28.4 | 41.1 | | |
| Worsened | 12.3 | 7.4 | | |
| Missing | 48.1 | 48.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ-5D-3L |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.07 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level in the Pain/Discomfort Dimension Responses at Cycle 6

| | |
|-----------------|---|
| End point title | Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level in the Pain/Discomfort Dimension Responses at Cycle 6 |
|-----------------|---|

End point description:

The EQ-5D-3L is a generic, self-administered questionnaire that consists of 5 dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has 3 levels of severity corresponding to no problems, some problems, and extreme problems. It also includes a Visual Analog Scale that recorded the respondent's self-rated health on a vertical, 0–100 scale, where 100 = Best imaginable health state and 0 = Worst imaginable health state. Distribution of the observed responses (i.e., no problems, moderate problems, severe problems, and missing) of the 5 dimensions at each visit was summarized per arm. The denominator for the percentage calculation per group was based on the number of the EQ-5D-3L evaluable population at baseline. The distribution of change in responses (i.e., improved [by ≥1 level], no change, worsened [by ≥1 level], and missing) from baseline are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 13.6 | 8.4 | | |
| No Change | 33.3 | 32.6 | | |
| Worsened | 4.9 | 10.5 | | |
| Missing | 48.1 | 48.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ-5D-3L |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.436 |
| Method | Fisher exact |

Secondary: Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level in the Anxiety/Depression Dimension Responses at Cycle 6

| | |
|-----------------|--|
| End point title | Percentage of Participants with Improved, Worsened, or No Change in the European Quality of Life–Five Dimension–Three Level in the Anxiety/Depression Dimension Responses at Cycle 6 |
|-----------------|--|

End point description:

The EQ-5D-3L is a generic, self-administered questionnaire that consists of 5 dimensions: mobility, self-care, pain, usual activities, and anxiety/depression. Each dimension has 3 levels of severity corresponding to no problems, some problems, and extreme problems. It also includes a Visual Analog Scale that recorded the respondent's self-rated health on a vertical, 0–100 scale, where 100 = Best imaginable health state and 0 = Worst imaginable health state. Distribution of the observed responses (i.e., no problems, moderate problems, severe problems, and missing) of the 5 dimensions at each visit was summarized per arm. The denominator for the percentage calculation per group was based on the number of the EQ-5D-3L evaluable population at baseline. The distribution of change in responses (i.e., improved [by ≥1 level], no change, worsened [by ≥1 level], and missing) from baseline are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline to Cycle 6 Day 1

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 81 | 95 | | |
| Units: Percentage of Participants | | | | |
| number (not applicable) | | | | |
| Improved | 4.9 | 7.4 | | |
| No Change | 35.8 | 37.9 | | |
| Worsened | 11.1 | 6.3 | | |
| Missing | 48.1 | 48.4 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ-5D-3L |
| Comparison groups | Placebo Plus Best Supportive Care v Oral Azacitidine Plus Best Supportive Care |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.683 |
| Method | Fisher exact |

Secondary: Healthcare Resource Utilization (HRU): Number of Participants Who Were Hospitalized During the Treatment Period

| | |
|-----------------|---|
| End point title | Healthcare Resource Utilization (HRU): Number of Participants Who Were Hospitalized During the Treatment Period |
|-----------------|---|

End point description:

The number of reasons for hospitalizations and hospital admissions during the treatment period were monitored and include those associated with: AEs, protocol-driven procedures, transfusions, non-protocol procedures, elective procedures or those associated with social, practical or technical reasons in the absence of AEs. HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization up to 28 days after the last dose of study drug; up to data cut off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Participants | | | | |
| Adverse Events | 79 | 65 | | |

| | | | | |
|--|----|----|--|--|
| Protocol Driven Procedures | 2 | 7 | | |
| Non-Protocol Driven Procedures | 9 | 19 | | |
| Transfusion | 32 | 33 | | |
| Procedure Planned Prior to Signing Consent | 0 | 4 | | |
| Elective Procedures | 4 | 10 | | |
| Social, Technical or Practical Reason except AEs | 4 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization (HRU): Total Number of Days Hospitalized Due to any Reason During the Treatment Period

| | |
|-----------------|--|
| End point title | Healthcare Resource Utilization (HRU): Total Number of Days Hospitalized Due to any Reason During the Treatment Period |
|-----------------|--|

End point description:

The total number of days hospitalized due to any reason during the treatment period was monitored. HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization up to 28 days after the last dose of study drug; up to data cut off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-----------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Days | 3513 | 2688 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization (HRU): Total Number of Days Hospitalized Per Total Patient-Years

| | |
|-----------------|--|
| End point title | Healthcare Resource Utilization (HRU): Total Number of Days Hospitalized Per Total Patient-Years |
|-----------------|--|

End point description:

The number of days hospitalized per total patient years. HRU was defined as any consumption of healthcare resources directly or indirectly related to the treatment of the patient.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From date of randomization up to 28 days after the last dose of study drug; up to data cut off date of 25 January 2019; median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| End point values | Oral Azacitidine Plus Best Supportive Care | Placebo Plus Best Supportive Care | | |
|-------------------------------------|--|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 109 | | |
| Units: Days Per Total Patient Years | | | | |
| number (not applicable) | 41.44 | 40.53 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for all-cause mortality from their randomization to study completion, (up to approximately 10 years). SAEs and Other AEs were assessed from first dose to 28 days following last dose (up to approximately 6 months)

Adverse event reporting additional description:

Median duration of treatment to oral azacitidine was 5.29 months and 5.36 months for placebo

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------|
| Reporting group title | CC-486 |
|-----------------------|--------|

Reporting group description:

Participants received 300 mg oral azacitidine tablets daily (QD) on days 1 to 21 of each 28-day treatment cycle and best supportive care (BSC) which included and was not limited to packed RBC (packed red blood cell [pRBC] and whole blood), platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and granulocyte colony stimulating factors (G-CSF) for participants who experienced neutropenic fever/infections.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received identically matching placebo tablets QD on days 1 to 21 of each 28-day treatment cycle and BSC which included but was not limited to, pRBC and whole blood, platelet transfusions (single donor or pooled donor), antibiotic, antiviral and/or antifungal therapy, nutritional support, and G-CSF for participants who experienced neutropenic fever/infections.

| Serious adverse events | CC-486 | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 83 / 107 (77.57%) | 69 / 109 (63.30%) | |
| number of deaths (all causes) | 83 | 86 | |
| number of deaths resulting from adverse events | 27 | 14 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bowen's disease | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone neoplasm | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (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 | 1 / 107 (0.93%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carcinoma in situ of skin | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system leukaemia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic myelomonocytic leukaemia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transformation to acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 6 / 109 (5.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord neoplasm | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestine carcinoma | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myelodysplastic syndrome with excess blasts | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 3 / 109 (2.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Metastases to liver | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mantle cell lymphoma recurrent | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm of unknown primary site | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal adenoma | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diffuse large B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteritis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyarteritis nodosa | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 107 (2.80%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypothermia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 107 (7.48%) | 4 / 109 (3.67%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Haemophagocytic lymphohistiocytosis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Prostatitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngeal oedema | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Bipolar disorder | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Injury, poisoning and procedural complications | | | |
| Arteriovenous fistula site haemorrhage | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis radiation | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 4 / 107 (3.74%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Febrile nonhaemolytic transfusion reaction | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transfusion reaction | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital haematoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (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 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haemorrhage | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 3 / 107 (2.80%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Long QT syndrome | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Presyncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| IIIrd nerve paresis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system lesion | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sciatica | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 107 (6.54%) | 5 / 109 (4.59%) | |
| occurrences causally related to treatment / all | 3 / 8 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Blood loss anaemia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 5 / 107 (4.67%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolytic anaemia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|-------------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 29 / 107 (27.10%) | 9 / 109 (8.26%) | |
| occurrences causally related to treatment / all | 28 / 45 | 4 / 13 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 107 (2.80%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 107 (2.80%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic colitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Intra-abdominal haemorrhage | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal achalasia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal varices haemorrhage | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral mucosal blistering | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cutaneous vasculitis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (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 | | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 3 / 109 (2.75%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prerenal failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Polychondritis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriovenous fistula site infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronavirus infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis escherichia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis clostridial | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemophilus infection | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymph gland infection | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis bacterial | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myringitis | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 5 / 107 (4.67%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 2 / 109 (1.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 13 / 107 (12.15%) | 12 / 109 (11.01%) | |
| occurrences causally related to treatment / all | 5 / 16 | 1 / 13 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumonia aspiration | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic abscess | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| 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 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 4 / 109 (3.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 8 / 107 (7.48%) | 3 / 109 (2.75%) | |
| occurrences causally related to treatment / all | 4 / 12 | 1 / 3 | |
| deaths causally related to treatment / all | 3 / 5 | 0 / 1 | |
| Septic shock | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 107 (5.61%) | 3 / 109 (2.75%) | |
| occurrences causally related to treatment / all | 3 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 3 / 5 | 1 / 3 | |
| Skin infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth abscess | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 107 (3.74%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 107 (1.87%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (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 | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic metabolic decompensation | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 107 (0.00%) | 1 / 109 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 107 (0.93%) | 0 / 109 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 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 | CC-486 | Placebo | |
|---|------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 107 / 107 (100.00%) | 104 / 109 (95.41%) | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 11 / 107 (10.28%) | 11 / 109 (10.09%) | |
| occurrences (all) | 11 | 17 | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 107 (4.67%) | 7 / 109 (6.42%) | |
| occurrences (all) | 5 | 7 | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 107 (5.61%) | 3 / 109 (2.75%) | |
| occurrences (all) | 7 | 3 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 25 / 107 (23.36%) | 20 / 109 (18.35%) | |
| occurrences (all) | 35 | 26 | |
| Fatigue | | | |
| subjects affected / exposed | 25 / 107 (23.36%) | 22 / 109 (20.18%) | |
| occurrences (all) | 32 | 29 | |
| Pyrexia | | | |
| subjects affected / exposed | 32 / 107 (29.91%) | 15 / 109 (13.76%) | |
| occurrences (all) | 48 | 27 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 30 / 107 (28.04%) | 17 / 109 (15.60%) | |
| occurrences (all) | 40 | 20 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 28 / 107 (26.17%) | 21 / 109 (19.27%) | |
| occurrences (all) | 58 | 34 | |
| Dyspnoea | | | |
| subjects affected / exposed | 14 / 107 (13.08%) | 15 / 109 (13.76%) | |
| occurrences (all) | 16 | 15 | |

| | | | |
|--|-------------------------|-------------------------|--|
| Cough subjects affected / exposed occurrences (all) | 16 / 107 (14.95%) 21 | 15 / 109 (13.76%) 19 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 11 / 107 (10.28%) 13 | 6 / 109 (5.50%) 6 | |
| Anxiety subjects affected / exposed occurrences (all) | 9 / 107 (8.41%) 10 | 4 / 109 (3.67%) 5 | |
| Confusional state subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 6 | 1 / 109 (0.92%) 1 | |
| Depression subjects affected / exposed occurrences (all) | 7 / 107 (6.54%) 7 | 2 / 109 (1.83%) 2 | |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 10 / 107 (9.35%) 11 | 6 / 109 (5.50%) 10 | |
| Weight decreased subjects affected / exposed occurrences (all) | 11 / 107 (10.28%) 13 | 3 / 109 (2.75%) 3 | |
| Serum ferritin increased subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 6 | 5 / 109 (4.59%) 5 | |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 9 | 1 / 109 (0.92%) 1 | |
| Contusion subjects affected / exposed occurrences (all) | 16 / 107 (14.95%) 21 | 3 / 109 (2.75%) 3 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |

| | | | |
|--|--------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 107 (6.54%) 10 | 2 / 109 (1.83%) 2 | |
| Cardiac failure subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 6 | 1 / 109 (0.92%) 1 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 8 / 107 (7.48%) 9 | 9 / 109 (8.26%) 10 | |
| Syncope subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 12 | 1 / 109 (0.92%) 1 | |
| Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) | 30 / 107 (28.04%) 59 | 18 / 109 (16.51%) 29 | |
| Neutropenia subjects affected / exposed occurrences (all) | 52 / 107 (48.60%) 116 | 16 / 109 (14.68%) 25 | |
| Leukopenia subjects affected / exposed occurrences (all) | 10 / 107 (9.35%) 18 | 3 / 109 (2.75%) 3 | |
| Anaemia subjects affected / exposed occurrences (all) | 23 / 107 (21.50%) 65 | 17 / 109 (15.60%) 41 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 16 / 107 (14.95%) 30 | 14 / 109 (12.84%) 17 | |
| Constipation subjects affected / exposed occurrences (all) | 51 / 107 (47.66%) 80 | 24 / 109 (22.02%) 39 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 6 / 107 (5.61%) 6 | 1 / 109 (0.92%) 1 | |
| Diarrhoea | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 73 / 107 (68.22%) | 26 / 109 (23.85%) | |
| occurrences (all) | 152 | 32 | |
| Gingival bleeding | | | |
| subjects affected / exposed | 7 / 107 (6.54%) | 4 / 109 (3.67%) | |
| occurrences (all) | 13 | 8 | |
| Nausea | | | |
| subjects affected / exposed | 81 / 107 (75.70%) | 25 / 109 (22.94%) | |
| occurrences (all) | 132 | 33 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 10 / 107 (9.35%) | 7 / 109 (6.42%) | |
| occurrences (all) | 13 | 12 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 4 / 107 (3.74%) | 6 / 109 (5.50%) | |
| occurrences (all) | 4 | 6 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 3 / 107 (2.80%) | 8 / 109 (7.34%) | |
| occurrences (all) | 3 | 11 | |
| Vomiting | | | |
| subjects affected / exposed | 67 / 107 (62.62%) | 11 / 109 (10.09%) | |
| occurrences (all) | 109 | 13 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 107 (5.61%) | 8 / 109 (7.34%) | |
| occurrences (all) | 6 | 10 | |
| Petechiae | | | |
| subjects affected / exposed | 21 / 107 (19.63%) | 20 / 109 (18.35%) | |
| occurrences (all) | 30 | 23 | |
| Ecchymosis | | | |
| subjects affected / exposed | 6 / 107 (5.61%) | 10 / 109 (9.17%) | |
| occurrences (all) | 6 | 17 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 4 / 107 (3.74%) | 6 / 109 (5.50%) | |
| occurrences (all) | 4 | 7 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Back pain | | | |
| subjects affected / exposed | 15 / 107 (14.02%) | 13 / 109 (11.93%) | |
| occurrences (all) | 17 | 16 | |
| Arthralgia | | | |
| subjects affected / exposed | 11 / 107 (10.28%) | 12 / 109 (11.01%) | |
| occurrences (all) | 15 | 15 | |
| Pain in extremity | | | |
| subjects affected / exposed | 8 / 107 (7.48%) | 4 / 109 (3.67%) | |
| occurrences (all) | 9 | 4 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 6 / 107 (5.61%) | 3 / 109 (2.75%) | |
| occurrences (all) | 7 | 3 | |
| Oral herpes | | | |
| subjects affected / exposed | 6 / 107 (5.61%) | 3 / 109 (2.75%) | |
| occurrences (all) | 6 | 3 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 107 (11.21%) | 5 / 109 (4.59%) | |
| occurrences (all) | 15 | 5 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 107 (6.54%) | 4 / 109 (3.67%) | |
| occurrences (all) | 11 | 4 | |
| Pneumonia | | | |
| subjects affected / exposed | 10 / 107 (9.35%) | 4 / 109 (3.67%) | |
| occurrences (all) | 13 | 6 | |
| Metabolism and nutrition disorders | | | |
| Iron overload | | | |
| subjects affected / exposed | 7 / 107 (6.54%) | 11 / 109 (10.09%) | |
| occurrences (all) | 8 | 11 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 11 / 107 (10.28%) | 5 / 109 (4.59%) | |
| occurrences (all) | 16 | 5 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 12 / 107 (11.21%) | 10 / 109 (9.17%) | |
| occurrences (all) | 21 | 11 | |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|-------------------|------------------|--|
| subjects affected / exposed | 6 / 107 (5.61%) | 0 / 109 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 6 / 107 (5.61%) | 2 / 109 (1.83%) | |
| occurrences (all) | 7 | 2 | |
| Decreased appetite | | | |
| subjects affected / exposed | 27 / 107 (25.23%) | 10 / 109 (9.17%) | |
| occurrences (all) | 36 | 10 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 21 February 2018 | The duration of the study and enrollment period was extended due to slow enrollment; Based on Food and Drug Administration (FDA) recommendation, for subjects in Cycle 1 or 2 as of 31 Jan 2018, dose schedule was reduced to 14 days; Based on DMC recommendation to enhance hematotoxicity monitoring, the following information was added to Section 8.2.4. Dose Modifications: "Any subject who experiences febrile neutropenia \geq Grade 3 will have IP held until fever has resolved; must be afebrile for 3 days before re-starting study drug. Administration of antibiotic, antiviral and antifungal therapy is strongly recommended"; Based on DMC recommendation, to enhance hematotoxicity monitoring, dose modification for neutropenia Grade 4 was updated; Based on DMC recommendation, to enhance hematotoxicity monitoring for Febrile Neutropenia, the following wording "Secondary prophylaxis with G-CSF may be considered" was changed to "Secondary prophylaxis with G-CSF is strongly recommended"; Based on DMC recommendation, to enhance hematotoxicity monitoring, Section 8.2.5. Re-treatment Criteria was updated to reflect that for subjects that experience hematotoxicity (absolute neutrophil count [ANC] or platelet drop to Grade 4, or 50% drop within Grade 4), hematologic recovery is required before starting the next cycle at Day 28. Hematology recovery is defined and a decision tree for hematologic recovery presents the rules in a friendly manner; Based on DMC recommendation, to enhance hematotoxicity monitoring, the following sentences were added: "Consider platelet transfusion if platelet counts are $< 25 \times 10^9/L$ "; Based on DMC recommendation, add information to enhance hematotoxicity monitoring. |
| 06 August 2018 | This protocol is being amended to address the sponsor's decision to close enrollment into the study and revise sample size. |
| 28 November 2018 | This protocol was amended to change the primary endpoint to RBC transfusion independence with duration ≥ 56 days (8 weeks) and to add an extension phase of CC-486 treatment once the trial is unblinded. |
| 24 May 2022 | Updated contact details for the Medical Monitor of the study; Therapeutic Area Head and their title were updated; New section added; Survival follow-up (FU) was updated by reducing the duration of survival FU to 35 days (± 7 days) after treatment discontinuation. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported