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 ≤ 75 × 10^9/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 (tfx) 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 particiapnts 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 Diffrence
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 ≥ 30 X 10^9/L for participants^ starting with > 20 X 10^9/L platelets; 2. Increase from < 20 X 10^9/L to > 20 X 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:

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.

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	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: 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 ≥1.0x10^9/L, platelets ≥100x10^9/dL, blasts (0%) • Partial Response (PR): same as CR bone marrow (BM) shows blasts decreased by ≥ 50% over pre-treatment but still > 5%; Cellularity and morphology

not relevant • Marrow CR: BM: ≤ 5% myeloblasts and decrease by ≥ 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: ≥ 50% increase in blasts to > 5% blasts - 5%-10% blasts:≥ 50% increase to > 10% blasts - 10%-20% blasts:≥ 50% increase to > 20% blasts - 20%-30% blasts ≥ 50% increase to > 30% blasts Any of the following: - ≥ 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: 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 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: 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: 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 azacitaidine 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 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 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 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 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 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:

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)	2.1 (± 8.74)	-0.6 (± 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 (± 17.29)	-2.7 (± 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 Improvment (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 Improvment (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 Raatio
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 Improvment (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 Improvment (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 Raatio
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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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 Improvment (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:

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

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