Clinical trial results:
ENHANCE: A Randomized, Double-blind, Multicenter Study Comparing Magrolimab in Combination with Azacitidine versus Azacitidine Plus Placebo in Treatment-naïve Patients with Higher Risk Myelodysplastic Syndrome

Summary

EudraCT number	2020-004287-26
Trial protocol	FR DE BE IE NL AT DK PT NO FI IT
Global end of trial date	18 July 2023

Results information

Result version number	v1 (current)
This version publication date	18 May 2024
First version publication date	18 May 2024

Trial information

Trial identification

Sponsor protocol code	5F9009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04313881
WHO universal trial number (UTN)	-
Other trial identifiers	Netherlands Registry ID: NL-OMON52320

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Clinical Trials Mailbox, Gilead Sciences International Ltd., clinical.trials@gilead.com
Scientific contact	Clinical Trials Mailbox, Gilead Sciences International Ltd., clinical.trials@gilead.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2023
Global end of trial reached?	Yes
Global end of trial date	18 July 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of magrolimab in combination with azacitidine compared to that of azacitidine plus placebo in previously untreated participants with intermediate/high/very high risk myelodysplastic syndrome (MDS) by Revised International Prognostic Scoring System (IPSS-R) as measured by complete remission (CR) and overall survival (OS).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.
This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 September 2020
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	Hong Kong: 8
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Türkiye: 2
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Australia: 75
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 21

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	United States: 352
Worldwide total number of subjects	539
EEA total number of subjects	83

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)	145
From 65 to 84 years	381
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Asia-Pacific Region, and Europe.

Pre-assignment

Screening details:

854 participants were screened.

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	Magrolimab + Azacitidine

Arm description:

Participants received the following magrolimab and azacitidine dosing regimens:
Magrolimab was administered as an intravenous (IV) priming dose of 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50). Following priming dose, magrolimab maintenance dose of 30 mg/kg was administered on Day 57 and 30 mg/kg every 2 weeks thereafter.
Azacitidine 75 mg/m^2 was administered either subcutaneously (SC) or IV on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each 28-day cycle.
The maximum duration of treatment was up to approximately 2.6 years.

Arm type	Experimental
Investigational medicinal product name	Magrolimab
Investigational medicinal product code	GS-4721
Other name	Hu5F9-G4
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Administered either subcutaneously or intravenously according to region-specific drug labeling.

Arm title	Placebo + Azacitidine

Arm description:

Participants received the following placebo dosing regimens to mirror magrolimab dosing regimen in addition to
azacitidine:
Placebo was administered as an IV on Days 1 and 4; Day 8; Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50). Additionally, placebo was administered on Day 57 and every 2 weeks thereafter.
Azacitidine 75 mg/m^2 was administered either SC or IV on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each 28-day cycle.
The maximum duration of treatment was up to approximately 2.5 years.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

Placebo to match magrolimab administered intravenously.

Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Administered either subcutaneously or intravenously according to region-specific drug labeling.

Number of subjects in period 1	Magrolimab + Azacitidine	Placebo + Azacitidine
Started	268	271
Completed	0	0
Not completed	268	271
Death	138	126
Study terminated by sponsor	108	129
Consent withdrawn	19	15
Reason not Specified	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Magrolimab + Azacitidine
Reporting group description:	
Participants received the following magrolimab and azacitidine dosing regimens: Magrolimab was administered as an intravenous (IV) priming dose of 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50). Following priming dose, magrolimab maintenance dose of 30 mg/kg was administered on Day 57 and 30 mg/kg every 2 weeks thereafter. Azacitidine 75 mg/m^2 was administered either subcutaneously (SC) or IV on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each 28-day cycle. The maximum duration of treatment was up to approximately 2.6 years.	
Reporting group title	Placebo + Azacitidine
Reporting group description:	
Participants received the following placebo dosing regimens to mirror magrolimab dosing regimen in addition to azacitidine: Placebo was administered as an IV on Days 1 and 4; Day 8; Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50). Additionally, placebo was administered on Day 57 and every 2 weeks thereafter. Azacitidine 75 mg/m^2 was administered either SC or IV on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each 28-day cycle. The maximum duration of treatment was up to approximately 2.5 years.	

Reporting group values	Magrolimab + Azacitidine	Placebo + Azacitidine	Total
Number of subjects	268	271	539
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	64	81	145
>=65 years	204	190	394
Age continuous Units: years			
arithmetic mean	70	68	
standard deviation	± 9.2	± 9.8	-
Gender categorical Units: Subjects			
Female	87	94	181
Male	181	177	358
Race Units: Subjects			
American Indian Or Alaska Native	0	0	0
Asian	14	14	28
Black or African American	11	9	20
Native Hawaiian Or Other Pacific Islander	0	0	0
White	209	207	416
Multiple	1	0	1
Not reported / Missing	33	41	74
Ethnicity Units: Subjects			

Not Hispanic or Latino	227	219	446
Hispanic or Latino	13	21	34
Unknown	5	7	12
Not Reported / Missing	23	24	47

End points

End points reporting groups

Reporting group title	Magrolimab + Azacitidine

Reporting group description:

Participants received the following magrolimab and azacitidine dosing regimens:
Magrolimab was administered as an intravenous (IV) priming dose of 1 mg/kg on Days 1 and 4; 15 mg/kg on Day 8; 30 mg/kg on Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50). Following priming dose, magrolimab maintenance dose of 30 mg/kg was administered on Day 57 and 30 mg/kg every 2 weeks thereafter.
Azacitidine 75 mg/m^2 was administered either subcutaneously (SC) or IV on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each 28-day cycle.
The maximum duration of treatment was up to approximately 2.6 years.

Reporting group title	Placebo + Azacitidine

Reporting group description:

Participants received the following placebo dosing regimens to mirror magrolimab dosing regimen in addition to
azacitidine:
Placebo was administered as an IV on Days 1 and 4; Day 8; Days 11, 15, followed by weekly administration for 5 doses (on Days 22, 29, 36, 43, and 50). Additionally, placebo was administered on Day 57 and every 2 weeks thereafter.
Azacitidine 75 mg/m^2 was administered either SC or IV on Days 1 to 7 (or Days 1 to 5 and 8 to 9) of each 28-day cycle.
The maximum duration of treatment was up to approximately 2.5 years.

Primary: Percentage of Participants With Complete Remission (CR)

End point title	Percentage of Participants With Complete Remission (CR)

End point description:

The percentage of participants (CR rate) are participants who reach morphologic CR (morphological blast of ≤ 5% and recovery of absolute neutrophil count (ANC), platelets, and hemoglobin from complete blood counts as well as peripheral blast) based on Investigator-assessed International Working Group (IWG) myelodysplastic syndrome (MDS) criteria on or prior to initiation of any new anticancer therapy, including stem cell therapy (SCT). Percentages were rounded off.
Participants from intent-to-treat (ITT) analysis set were analyzed. The ITT Analysis Set included all participants who were randomized in the study, with treatment assignments designated according to the treatment that participants were randomized to.

End point type	Primary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: percentage of participants				
number (confidence interval 95%)	21.3 (16.5 to 26.7)	23.6 (18.7 to 29.1)		

Statistical analyses

Statistical analysis title	Statistical analysis of CR
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.5218
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.876
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.585
upper limit	1.312

Notes:

[1] - 2-sided P-value, odds ratio and its 95% CI were based on Cochran-Mantel-Haenszel (CMH) method stratified by stratification factors (geographic region, cytogenetic risk status, and bone marrow blast percentage).

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the number of months measured from the date of randomization to the date of death from any cause. Kaplan Meier (KM) estimates were used for analysis.
Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.

End point type	Primary

End point timeframe:

From randomization up to 32.62 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: months				
median (confidence interval 95%)	15.9 (13.3 to 19.5)	18.6 (14.9 to 26.2)		

Statistical analyses

Statistical analysis title	Statistical analysis of OS
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.1299
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.203
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.947
upper limit	1.528

Notes:

[2] - 2-sided P-value was based on stratified log-rank test, stratified by stratification factors. Hazard ratio and its 95% confidence interval (CI) were calculated using the Cox proportional hazards regression model, stratified by stratification factors.

Secondary: Duration of CR (DOCR)

End point title	Duration of CR (DOCR)

End point description:

DOCR=Time from first CR date to first relapse date, disease progression (PD) or death, prior to initiation of any new anticancer therapy excluding SCT whichever occurs earlier.
PD is defined as: <5% blasts: ≥50 increase in blasts to >5% blasts,5%-10% blasts: ≥50% increase in blasts to >10% blasts, 10%-20% blasts: ≥50% increase in blasts to >20% blasts,20%-30% blasts: ≥50% increase in blasts to >30% blasts, any of the following: at least 50% decrease from maximum remission/response in granulocytes or platelets. Reduction in Hgb by ≥2 g/dL / Transfusion dependence. Relapse= return to pretreatment bone marrow blast percentage / decrease of ≥ 50% from maximum remission/response levels in granulocytes or platelets/ reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence. CR is defined in end point 1. KM estimates were used for analysis.Participants from ITT who achieved CR were analyzed. 9999= Upper limit of CI was not estimable due to low number of participants with events

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	64		
Units: months				
median (confidence interval 95%)	10.9 (8.9 to 16.7)	11.1 (8.1 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants who reach objective response including CR, partial remission (PR), marrow CR or hematological improvement prior to initiation of any new anticancer therapy including SCT for MDS per IWG 2006 criteria per investigator's evaluation. CR is defined in outcome measure 1.
PR is defined as all CR criteria if abnormal before treatment except, one marrow blasts decreased by ≥ 50% over pretreatment but still > 5% cellularity and morphology not relevant.
Marrow CR is defined as bone marrow ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment, stable disease with any hematological improvement, peripheral blood: if hematological improvement responses, they were noted in addition to marrow CR.
Stable Disease: Failure to achieve at least PR, but no evidence of progression for > 8 weeks.
Percentages were rounded off.
Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: percentage of participants				
number (confidence interval 95%)	53.7 (47.6 to 59.8)	58.7 (52.6 to 64.6)		

Statistical analyses

Statistical analysis title	Statistical analysis of ORR
Comparison groups	Placebo + Azacitidine v Magrolimab + Azacitidine
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.2563
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.821
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.584
upper limit	1.155

Notes:

[3] - 2-sided P-value, odds ratio and its 95% CI were based on Cochran-Mantel-Haenszel (CMH) method stratified by stratification factors (geographic region, cytogenetic risk status and bone marrow blast percentage).

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is measured from time measurement criteria are first met for objective response to first date of relapse, disease progression (PD) /death, prior to initiation of any new anticancer therapy excluding SCT

whichever occurs earlier. Disease progression and relapse have been defined in end point number 3. KM estimates were used for analysis.
Analysis Population Description: Participants from intent-to-treat analysis set with objective response were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	159		
Units: months				
median (confidence interval 95%)	10.1 (8.1 to 12.5)	10.2 (7.6 to 12.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Red Blood Cell (RBC) Transfusion Independence Rate

End point title	Red Blood Cell (RBC) Transfusion Independence Rate

End point description:

RBC transfusion independence rate is defined as the percentage of participants who have a 56-day or longer period with no RBC transfusions at any time between randomization and initiation of any new anticancer therapy, including SCT, among all participants who were RBC transfusion-dependent at Baseline. Percentages were rounded off.
Analysis Population Description: Participants from intent-to-treat analysis set who were RBC transfusion-dependent at baseline were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	125		
Units: percentage of participants				
number (confidence interval 95%)	27.9 (20.6 to 36.1)	35.2 (26.9 to 44.2)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2191 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.427
upper limit	1.212

Notes:

[4] - 95% CI for transfusion independence rate was based on Clopper-Pearson exact method. 2-sided P-value, odds ratio and its 95% CI were based on Cochran-Mantel-Haenszel (CMH) method stratified by stratification factors.

Secondary: Event Free Survival (EFS)

End point title	Event Free Survival (EFS)

End point description:

EFS is defined as the time from randomization to transformation to acute myeloid leukemia (AML) or death from any cause, whichever occurs first. Transformation assessments and deaths post SCT were included in the analysis. KM estimates were used for analysis. Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: months				
median (confidence interval 95%)	13.0 (10.2 to 15.9)	12.9 (10.8 to 14.6)		

Statistical analyses

Statistical analysis title	Statistical analysis of EFS
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine

Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.8788 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.979
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	1.285

Notes:

[5] - Hazard ratio and its 95% CI were calculated using the Cox proportional hazards regression model, stratified by stratification factors.

[6] - 2-sided P-value was based on stratified log-rank test, stratified by stratification factors.

Secondary: Percentage of Participants With CR in Participants With TP53 Mutation

End point title	Percentage of Participants With CR in Participants With TP53 Mutation

End point description:

CR in TP53 mutant population is defined as the percentage of participants who achieve a morphologic CR based on investigator assessments using IWG criteria on or prior to initiation of any new anticancer therapy, including SCT in TP53 mutant population. Percentages were rounded off. Participants from intent-to-treat analysis set with TP53 mutation were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	64		
Units: percentage of participants				
number (confidence interval 95%)	17.7 (10.0 to 27.9)	32.8 (21.6 to 45.7)		

Statistical analyses

Statistical analysis title	Statistical analysis of CR rate
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0375 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.441

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.203
upper limit	0.96

Notes:

[7] - 2-sided P-value, odds ratio and its 95% CI were based on unstratified Cochran-Mantel- Haenszel (CMH) method.
[8] - 95% CI for response rate was based on Clopper-Pearson exact method.

Secondary: Minimal Residual Disease (MRD)-Negative Response Rate

End point title	Minimal Residual Disease (MRD)-Negative Response Rate

End point description:

The MRD-negative response rate is defined as the percentage of participants who achieved a morphologic CR or marrow CR based on Investigator-assessed IWG criteria and reached MRD-negative disease status prior to initiation of any new anticancer therapy, including SCT. MRD-negative disease status was assessed using a multiparameter flow cytometry-based assay performed by a central laboratory. Morphologic CR and marrow CR are defined in endpoint 1 and 4, respectively. Percentages were rounded off.
Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: percentage of participants				
number (confidence interval 95%)	21.6 (16.9 to 27.1)	22.5 (17.7 to 28.0)		

Statistical analyses

Statistical analysis title	Statistical analysis of MRD-Negative Response Rate
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.795
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.947
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.629
upper limit	1.426

Notes:

[9] - 2-sided P-value, odds ratio and its 95% CI were based on Cochran-Mantel-Haenszel (CMH) method stratified by stratification factors (geographic region, cytogenetic risk status and bone marrow blast percentage).

Secondary: Time to Transformation to AML

End point title	Time to Transformation to AML

End point description:

Time to transformation to AML is defined as the time from randomization to the collection date of bone marrow sample leading to documented AML diagnosis. Transformation assessments post SCT were included in the analysis. KM estimates were used for analysis. Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.
9999 = Median and upper limit of CI was not estimable due to low number of participants with events.
9999 = Upper limit of CI was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: months				
median (confidence interval 95%)	9999 (21.2 to 9999)	25.5 (25.5 to 9999)		

Statistical analyses

Statistical analysis title	Statistical analysis ofTimetoTransformation to AML
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.461
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.522
upper limit	1.343

Notes:

[10] - 2-sided P-value was based on stratified log-rank test, stratified by stratification factors. Hazard ratio and its 95% CI were calculated using the Cox proportional hazards regression model, stratified by stratification factors.

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is defined as the time from randomization to the date of documented DP (including treatment failure by IWG criteria or relapse after PR/CR), or death from any cause, whichever occurs first. Response assessments and deaths post SCT were included in the analysis. Treatment failure is defined as, Death during treatment or disease progression characterized by worsening cytopenia, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment. Relapse after CR or PR = Return to pretreatment bone marrow blast percentage / Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets / Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence.
CR, PR and PD are defined in end points 1, 4 and 5 respectively. KM estimates were used for analysis.
Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.

End point type	Secondary

End point timeframe:

From randomization up to 31.01 months

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: months				
median (confidence interval 95%)	9.0 (8.3 to 10.9)	9.4 (8.6 to 11.4)		

Statistical analyses

Statistical analysis title	Statistical analysis of PFS
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.872
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.802
upper limit	1.297

Notes:

[11] - 2-sided P-value was based on stratified log-rank test, stratified by stratification factors (geographic region, cytogenetic risk status, and bone marrow blast percentage). Hazard ratio and its 95% CI were calculated using the Cox proportional hazards regression model, stratified by stratification factors.

Secondary: Functional Assessment of Cancer Therapy-Anemia (FACT-Anemia) Response Rate

End point title	Functional Assessment of Cancer Therapy-Anemia (FACT-Anemia) Response Rate

End point description:

The FACT-Anemia response rate is defined as the percentage of participants who showed clinically meaningful improvement in health-related quality of life (HRQoL) based on the score from the FACT-Anemia instrument prior to initiation of any new anticancer therapy, including SCT. The minimal clinically meaningful difference of 7.0 was used as cutoff for clinically meaningful improvement.
The FACT-Anemia instrument consists of 5 subscales, including physical well-being, emotional well-being, functional well-being, social well-being, and anemia symptoms. Each subscale measures items on a 5-point Likert scale from 0 to 4, where 0 = not at all and 4 = very much. The subscales are scored by summing points from all questions, then converting this sum to a 100 point scale; 0 indicates the poorest quality of life (QOL) and 100 denotes the highest QOL. Percentages were rounded off.
Analysis Population Description: Participants from intent-to-treat analysis set were analyzed.

End point type	Secondary

End point timeframe:

Up to week 136

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268	271		
Units: percentage of participants				
number (confidence interval 95%)	37.7 (31.9 to 43.8)	49.8 (43.7 to 55.9)		

Statistical analyses

Statistical analysis title	Statistical analysis of FACT-Anemia Response Rate
Comparison groups	Magrolimab + Azacitidine v Placebo + Azacitidine
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0048
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.605
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.428
upper limit	0.857

Notes:

[12] - 2-sided P-value, odds ratio and its 95% CI were based on Cochran-Mantel-Haenszel (CMH) method stratified by stratification factors (geographic region, cytogenetic risk status, and bone marrow blast percentage).

Secondary: Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAE)

End point title	Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAE)

End point description:

TEAE's are defined as any AEs with an onset date on or after the study drug start date, no later than 70

days after study drug last dose date or day before initiation of new anticancer therapy including SCT. If AE onset date is on or before last dose date, it is considered as TEAE regardless of start of new anticancer therapy. An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with use of an investigational product or other protocol imposed intervention, regardless of attribution. An event is considered "serious", if it results death, life-threatening, inpatient or prolongation hospitalization, incapacity or substantial disruption of the ability to conduct normal functions, a congenital anomaly/birth defect, and important medical events. Participants from safety analysis set with data available were analyzed. Safety analysis set included all randomized participants who took at least 1 dose of any study treatment.

End point type	Secondary

End point timeframe:

First dose date up to 135.9 weeks plus 70 days (Up to 2.8 years)

End point values	Magrolimab + Azacitidine	Placebo + Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	264		
Units: percentage of participants				
number (not applicable)				
TEAE	100	99.6		
Serious TEAE	71.9	51.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Magrolimab

End point title	Serum Concentration of Magrolimab[13]

End point description:

Pretreatment assessments for the initial dose may be collected up to 72 hours before administration of study treatment; thereafter, pretreatment assessments are to be collected within 24 hours prior to study treatment administration.
Analysis Population Description: Pharmacokinetic (PK) analysis set included all participants who took at least 1 dose of magrolimab and had at least 1 measurable post-treatment serum concentration of magrolimab. Participants with data available at the given timepoint were analyzed.

End point type	Secondary

End point timeframe:

Preinfusion on Days 0, 7, 28, 56, 112, 168, 252 and 336

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis were not available for this endpoint.

End point values	Magrolimab + Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	218			
Units: µg/mL				
arithmetic mean (standard deviation)				
Preinfusion Day 0 (n=216)	0 (± 0)			

Preinfusion Day 7 (n=205)	1.09 (± 15.575)			
Preinfusion Day 28 (n=197)	500.13 (± 256.129)			
Preinfusion Day 56 (n=180)	612.53 (± 315.037)			
Preinfusion Day 112 (n=125)	295.64 (± 178.952)			
Preinfusion Day 168 (n=88)	258.70 (± 150.259)			
Preinfusion Day 252 (n=58)	299.63 (± 168.944)			
Preinfusion Day 336 (n=42)	336.57 (± 241.789)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Positive Anti-magrolimab Antibodies

End point title	Percentage of Participants With Positive Anti-magrolimab Antibodies[14]

End point description:

Percentages were rounded off.
Analysis Population Description: Participants in Immunogenicity Analysis Set with at least 1 baseline anti-drug antibody (ADA) sample and at least post-treatment ADA Sample were analyzed.
Immunogenicity Analysis Set includes participants who took at least 1 dose of magrolimab and have at least 1 reported ADA result.

End point type	Secondary

End point timeframe:

Up to 72 hours before administration of any treatment at Day 1, Cycle 1; within 24 hours prior to any study drug administration at Day 1 of Cycles 2, 3, 5, 7, 10, and 13 and End of Treatment (± 7 Days after last study drug dose); Cycle length is 28 Days

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Statistical analysis were not available for this endpoint.

End point values	Magrolimab + Azacitidine			
Subject group type	Reporting group			
Number of subjects analysed	230			
Units: percentage of participants				
number (not applicable)	3.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 135.9 weeks plus 70 days (Up to 2.8 years)

Adverse event reporting additional description:

All cause mortality: The ITT analysis set included all participants who were randomized in the study, with treatment assignments designated according to the treatment that participants were randomized to.
Adverse Events: The safety analysis set included all randomized participants who received at least 1 dose of any study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo + Azacitidine

Reporting group description:

Patients who received Placebo + Azacitidine

Reporting group title	Magrolimab + Azacitidine

Reporting group description:

Patients who received Magrolimab + Azacitidine

Serious adverse events	Placebo + Azacitidine	Magrolimab + Azacitidine	
Total subjects affected by serious adverse events			
subjects affected / exposed	136 / 264 (51.52%)	189 / 263 (71.86%)	
number of deaths (all causes)	132	145	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vasculitis			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	6 / 264 (2.27%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	1 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure inadequately ~ controlled			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive ~ disease			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	16 / 264 (6.06%)	17 / 263 (6.46%)	
occurrences causally related to treatment / all	5 / 19	4 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 264 (1.52%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 264 (0.00%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oedema peripheral			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health ~ deterioration			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site irritation			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Swelling face			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response ~ syndrome			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 264 (0.38%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 264 (0.38%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 264 (0.38%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 264 (1.14%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 264 (1.14%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 4	
Laryngeal oedema			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 264 (0.00%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 264 (0.76%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 264 (0.00%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 264 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia test positive			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio ~ increased			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 264 (0.38%)	31 / 263 (11.79%)	
occurrences causally related to treatment / all	1 / 1	34 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	2 / 264 (0.76%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 264 (0.00%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile nonhaemolytic transfusion ~ reaction			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular procedure complication			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 264 (0.38%)	6 / 263 (2.28%)	
occurrences causally related to treatment / all	0 / 1	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 264 (0.00%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus bradycardia			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Angina pectoris			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
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 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
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	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	4 / 264 (1.52%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Stress cardiomyopathy			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 264 (1.14%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	3 / 264 (1.14%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Seizure			
subjects affected / exposed	1 / 264 (0.38%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoid sinus thrombosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iiird nerve paralysis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (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 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Presyncope			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	44 / 264 (16.67%)	58 / 263 (22.05%)	
occurrences causally related to treatment / all	26 / 67	41 / 87	
deaths causally related to treatment / all	0 / 1	1 / 2	
Haemolysis			
subjects affected / exposed	0 / 264 (0.00%)	9 / 263 (3.42%)	
occurrences causally related to treatment / all	0 / 0	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	7 / 264 (2.65%)	25 / 263 (9.51%)	
occurrences causally related to treatment / all	3 / 8	26 / 32	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 264 (0.38%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cold type haemolytic anaemia			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravascular haemolysis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell agglutination			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 264 (1.14%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 264 (1.14%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	1 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	3 / 264 (1.14%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 264 (0.38%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	1 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 264 (1.14%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	3 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 264 (0.76%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			

subjects affected / exposed	2 / 264 (0.76%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (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 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematochezia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
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	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth swelling			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatosplenomegaly			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 264 (0.76%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle mass			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle necrosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 264 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			

subjects affected / exposed	10 / 264 (3.79%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 4	0 / 1	
Pneumonia			
subjects affected / exposed	11 / 264 (4.17%)	24 / 263 (9.13%)	
occurrences causally related to treatment / all	4 / 12	9 / 27	
deaths causally related to treatment / all	0 / 1	1 / 7	
Sepsis			
subjects affected / exposed	13 / 264 (4.92%)	20 / 263 (7.60%)	
occurrences causally related to treatment / all	4 / 15	6 / 21	
deaths causally related to treatment / all	1 / 5	0 / 7	
Cellulitis			
subjects affected / exposed	7 / 264 (2.65%)	4 / 263 (1.52%)	
occurrences causally related to treatment / all	3 / 8	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	4 / 264 (1.52%)	6 / 263 (2.28%)	
occurrences causally related to treatment / all	2 / 4	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urinary tract infection			
subjects affected / exposed	2 / 264 (0.76%)	7 / 263 (2.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 264 (0.76%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	1 / 2	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 264 (0.38%)	6 / 263 (2.28%)	
occurrences causally related to treatment / all	2 / 4	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulitis			

subjects affected / exposed	1 / 264 (0.38%)	5 / 263 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	2 / 264 (0.76%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 264 (0.38%)	3 / 263 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Covid-19 pneumonia			
subjects affected / exposed	2 / 264 (0.76%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacterial infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (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 / 264 (0.00%)	1 / 263 (0.38%)	
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 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hcov-oc43 infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site cellulitis			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injection site cellulitis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node tuberculosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucormycosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural cellulitis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Azacitidine	Magrolimab + Azacitidine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	256 / 264 (96.97%)	246 / 263 (93.54%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 264 (5.68%)	16 / 263 (6.08%)	
occurrences (all)	37	22	
Hypotension			
subjects affected / exposed	22 / 264 (8.33%)	42 / 263 (15.97%)	
occurrences (all)	26	48	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	101 / 264 (38.26%)	105 / 263 (39.92%)	
occurrences (all)	139	138	
Pyrexia			
subjects affected / exposed	39 / 264 (14.77%)	75 / 263 (28.52%)	
occurrences (all)	49	107	
Oedema peripheral			
subjects affected / exposed	46 / 264 (17.42%)	62 / 263 (23.57%)	
occurrences (all)	53	73	
Chills			
subjects affected / exposed	22 / 264 (8.33%)	41 / 263 (15.59%)	
occurrences (all)	26	52	
Injection site reaction			
subjects affected / exposed	26 / 264 (9.85%)	18 / 263 (6.84%)	
occurrences (all)	31	19	
Asthenia			
subjects affected / exposed	15 / 264 (5.68%)	22 / 263 (8.37%)	
occurrences (all)	18	31	
Non-cardiac chest pain			
subjects affected / exposed	14 / 264 (5.30%)	14 / 263 (5.32%)	
occurrences (all)	15	21	
Pain			
subjects affected / exposed	12 / 264 (4.55%)	14 / 263 (5.32%)	
occurrences (all)	12	14	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	42 / 264 (15.91%)	57 / 263 (21.67%)	
occurrences (all)	54	70	
Cough			
subjects affected / exposed	38 / 264 (14.39%)	55 / 263 (20.91%)	
occurrences (all)	45	62	
Epistaxis			
subjects affected / exposed	34 / 264 (12.88%)	27 / 263 (10.27%)	
occurrences (all)	39	34	
Oropharyngeal pain			

subjects affected / exposed	15 / 264 (5.68%)	21 / 263 (7.98%)	
occurrences (all)	16	26	
Pleural effusion			
subjects affected / exposed	10 / 264 (3.79%)	20 / 263 (7.60%)	
occurrences (all)	11	20	
Nasal congestion			
subjects affected / exposed	16 / 264 (6.06%)	7 / 263 (2.66%)	
occurrences (all)	19	7	
Hypoxia			
subjects affected / exposed	11 / 264 (4.17%)	14 / 263 (5.32%)	
occurrences (all)	12	15	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	30 / 264 (11.36%)	35 / 263 (13.31%)	
occurrences (all)	31	43	
Anxiety			
subjects affected / exposed	19 / 264 (7.20%)	24 / 263 (9.13%)	
occurrences (all)	20	24	
Investigations			
Platelet count decreased			
subjects affected / exposed	64 / 264 (24.24%)	71 / 263 (27.00%)	
occurrences (all)	122	188	
Neutrophil count decreased			
subjects affected / exposed	59 / 264 (22.35%)	67 / 263 (25.48%)	
occurrences (all)	132	190	
White blood cell count decreased			
subjects affected / exposed	41 / 264 (15.53%)	47 / 263 (17.87%)	
occurrences (all)	99	127	
Blood bilirubin increased			
subjects affected / exposed	8 / 264 (3.03%)	27 / 263 (10.27%)	
occurrences (all)	12	40	
Alanine aminotransferase increased			
subjects affected / exposed	15 / 264 (5.68%)	19 / 263 (7.22%)	
occurrences (all)	20	20	
Lymphocyte count decreased			

subjects affected / exposed	13 / 264 (4.92%)	18 / 263 (6.84%)	
occurrences (all)	35	53	
Blood creatinine increased			
subjects affected / exposed	16 / 264 (6.06%)	13 / 263 (4.94%)	
occurrences (all)	25	21	
Weight decreased			
subjects affected / exposed	11 / 264 (4.17%)	18 / 263 (6.84%)	
occurrences (all)	11	20	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 264 (4.92%)	14 / 263 (5.32%)	
occurrences (all)	19	14	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	21 / 264 (7.95%)	29 / 263 (11.03%)	
occurrences (all)	25	38	
Infusion related reaction			
subjects affected / exposed	40 / 264 (15.15%)	72 / 263 (27.38%)	
occurrences (all)	43	98	
Contusion			
subjects affected / exposed	34 / 264 (12.88%)	31 / 263 (11.79%)	
occurrences (all)	50	38	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	9 / 264 (3.41%)	17 / 263 (6.46%)	
occurrences (all)	10	17	
Sinus tachycardia			
subjects affected / exposed	14 / 264 (5.30%)	12 / 263 (4.56%)	
occurrences (all)	21	13	
Palpitations			
subjects affected / exposed	7 / 264 (2.65%)	16 / 263 (6.08%)	
occurrences (all)	8	22	
Nervous system disorders			
Headache			
subjects affected / exposed	60 / 264 (22.73%)	49 / 263 (18.63%)	
occurrences (all)	76	74	
Dizziness			

subjects affected / exposed	46 / 264 (17.42%)	46 / 263 (17.49%)	
occurrences (all)	60	58	
Dysgeusia			
subjects affected / exposed	13 / 264 (4.92%)	19 / 263 (7.22%)	
occurrences (all)	14	22	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	60 / 264 (22.73%)	63 / 263 (23.95%)	
occurrences (all)	127	190	
Anaemia			
subjects affected / exposed	75 / 264 (28.41%)	124 / 263 (47.15%)	
occurrences (all)	145	278	
Febrile neutropenia			
subjects affected / exposed	14 / 264 (5.30%)	14 / 263 (5.32%)	
occurrences (all)	18	14	
Thrombocytopenia			
subjects affected / exposed	46 / 264 (17.42%)	54 / 263 (20.53%)	
occurrences (all)	71	133	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	150 / 264 (56.82%)	144 / 263 (54.75%)	
occurrences (all)	184	187	
Nausea			
subjects affected / exposed	114 / 264 (43.18%)	133 / 263 (50.57%)	
occurrences (all)	150	179	
Diarrhoea			
subjects affected / exposed	89 / 264 (33.71%)	102 / 263 (38.78%)	
occurrences (all)	125	164	
Vomiting			
subjects affected / exposed	55 / 264 (20.83%)	53 / 263 (20.15%)	
occurrences (all)	74	69	
Abdominal pain			
subjects affected / exposed	25 / 264 (9.47%)	39 / 263 (14.83%)	
occurrences (all)	27	46	
Stomatitis			

subjects affected / exposed	25 / 264 (9.47%)	22 / 263 (8.37%)	
occurrences (all)	29	26	
Haemorrhoids			
subjects affected / exposed	15 / 264 (5.68%)	13 / 263 (4.94%)	
occurrences (all)	15	13	
Oral pain			
subjects affected / exposed	9 / 264 (3.41%)	17 / 263 (6.46%)	
occurrences (all)	10	17	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	25 / 264 (9.47%)	31 / 263 (11.79%)	
occurrences (all)	27	37	
Rash			
subjects affected / exposed	21 / 264 (7.95%)	19 / 263 (7.22%)	
occurrences (all)	24	20	
Rash maculo-papular			
subjects affected / exposed	16 / 264 (6.06%)	18 / 263 (6.84%)	
occurrences (all)	23	20	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	47 / 264 (17.80%)	41 / 263 (15.59%)	
occurrences (all)	50	45	
Muscular weakness			
subjects affected / exposed	24 / 264 (9.09%)	26 / 263 (9.89%)	
occurrences (all)	26	32	
Pain in extremity			
subjects affected / exposed	28 / 264 (10.61%)	20 / 263 (7.60%)	
occurrences (all)	30	25	
Back pain			
subjects affected / exposed	21 / 264 (7.95%)	24 / 263 (9.13%)	
occurrences (all)	23	29	
Muscle spasms			
subjects affected / exposed	14 / 264 (5.30%)	13 / 263 (4.94%)	
occurrences (all)	15	13	
Neck pain			

subjects affected / exposed	17 / 264 (6.44%)	6 / 263 (2.28%)	
occurrences (all)	17	6	
Infections and infestations			
Covid-19			
subjects affected / exposed	22 / 264 (8.33%)	23 / 263 (8.75%)	
occurrences (all)	23	23	
Pneumonia			
subjects affected / exposed	8 / 264 (3.03%)	21 / 263 (7.98%)	
occurrences (all)	8	23	
Urinary tract infection			
subjects affected / exposed	13 / 264 (4.92%)	14 / 263 (5.32%)	
occurrences (all)	16	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	47 / 264 (17.80%)	72 / 263 (27.38%)	
occurrences (all)	48	80	
Hypokalaemia			
subjects affected / exposed	31 / 264 (11.74%)	50 / 263 (19.01%)	
occurrences (all)	40	71	
Hypophosphataemia			
subjects affected / exposed	20 / 264 (7.58%)	23 / 263 (8.75%)	
occurrences (all)	23	27	
Hypomagnesaemia			
subjects affected / exposed	21 / 264 (7.95%)	17 / 263 (6.46%)	
occurrences (all)	26	29	
Hyponatraemia			
subjects affected / exposed	18 / 264 (6.82%)	18 / 263 (6.84%)	
occurrences (all)	32	34	
Hyperglycaemia			
subjects affected / exposed	15 / 264 (5.68%)	19 / 263 (7.22%)	
occurrences (all)	30	30	
Hypoalbuminaemia			
subjects affected / exposed	14 / 264 (5.30%)	20 / 263 (7.60%)	
occurrences (all)	24	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2020	Protocol 5F9009 amended to update the sample size, study design, and statistical analysis to ensure robust comparison of magrolimab plus azacitidine versus azacitidine plus placebo with respect to both complete remission rate and overall survival. Furthermore, recent acquisition of Forty Seven Inc. by Gilead Sciences, Inc., the amendment is intended to reflect this change in study sponsor and to include key elements from the Gilead protocol template.
07 January 2021	In Amendment 3, the following has been amended: Section 2.1.6: reference pandemic mitigation plan in Appendix I and confirm that an acceptable risk-benefit ratio was maintained. Section 4.7, Inclusion Criterion 1 updated to specify exclusion of MDS patients who required AML like therapy in accordance with European Society for Medical Oncology Clinical Practice, Guidelines for MDS diagnosis, treatment, and follow-up. Inclusion Criterion 9 updated to require AST and ALT to be ≤ 3 × ULN instead of ≤ 5 ´ ULN. Inclusion Criterion 12 and Inclusion Criterion 13 were consolidated into Criterion 12. Section 4.8, Exclusion Criteria 11 and 12 have replaced the previous Exclusion Criterion 11 in order to provide additional details with respect to investigator assessment of known HIV, hepatitis B, and hepatitis C infection. Section 4.9.1 and 4.9.2 updated to remove contraception language details and instead reference Appendix H. Section 5.7.1 and Section 6.4, language regarding permitting treatment with magrolimab/placebo alone or azacitidine alone if the other study treatment was discontinued has been removed. Section 5.7.1, updated with additional guidance for investigators when considering stem cell transplant for patients who achieve response on study treatment. Section 6.8.3, updated to clarify procedures for unblinding a patient's treatment assignment to treating physician only in event of a medical emergency, and to add a designated unblinded role at Sponsor Clinical Operations post Protocol Amendment 2. Section 6.9.2, updated to include non-clinical and clinical safety information with respect to concomitant magrolimab and hydroxyurea. Section 7.2.7, updated for hospitalization scenarios that did not require SAE reporting. Section 7.10.1.4, added as new section to provide clinical management guidelines and discontinuation criteria to support risk minimization of pneumonitis. Appendix H, Section 2 and 3 were edited for consistency.

04 February 2021	In Amendment 4, Protocol 5F9009 amended to clarify and ensure consistency between sections. Updates to the protocol include the following: Section 4.3 and Table 2 (Schedule of Assessments - Screening) were updated to add hepatitis B and C and HIV testing for all patients as part of the screening procedure to ensure that the exclusion criterion is met. Section 4.8, Exclusion Criterion 3 was added to exclude patients determined by then investigator to be eligible for an allogeneic SCT with an available donor and who can be transplanted immediately. This change made to reflect that allogeneic stem cell transplantation should always be sought and performed when this option is immediately available to patients. Section 4.8, Exclusion Criteria 12 and 13 have replaced the previous Exclusion Criteria 11 and 12 to exclude patients with known hepatitis B or C infection or HIV infection in medical history or following testing at screening. Section 5.2 Table 6 was changed to reflect required assessments at screening. Section 6.4 was updated to state all patients monitored hourly during infusion. Patients monitored (including measurement of vital signs, as clinically appropriate) for signs and symptoms of infusion related reactions, which have been observed in previous magrolimab studies. Multiple sections (Section 4.3 Table 4, and Sections 5, 5.1.10, 5.1.11, 5.7.1, 6.9.2, 7.7.2, 7.7.3) were updated to extend safety follow-up to 70 days or 5 elimination half-lives of magrolimab. Section 6.7.2.2.1, Table 10 was corrected to reflect azacitidine dose modifications in the current azacitidine labeling information.
18 August 2021	In Amendment 5, the following has been amended: Sections 2.1.2.1, 4.1, 4.2, 4.3 (Tables 3 and 5- Schedule of Assessments), 6.1 (Table 8), and 6.4 were updated and Table 4 was newly added. Section 4.3, Table 3 and 5 (Schedule of Assessments) footnote updated. Section 4.8 – inclusion criterion 1 and exclusion criterion 2 were updated. Section 5 and 5.7.1, updated to clarify the language around the 30-day and 70-day safety follow-up. Sections 5.1.4, and 7.10.1, updated to simplify the language for the blood type and screen assessment. Section 5.1.10, updated to clarify the reporting of adverse events. Section 5.1.11, added to provide guidance regarding concomitant use of the coronavirus disease 2019 (COVID-19) vaccine, specifically while there was no contraindication of magrolimab and azacitidine with the COVID-19 vaccine, investigators should use clinical judgement when deciding to administer the vaccine to participants on study. Section 5.3, updated with additional guidance for assessment of complete response (CR). Section 5.6.3, updated to clarify requirements for bone marrow biopsies. Section 6.4, updated to provide updated information regarding duration of infusion. Sections 6.4, 6.7.1.1, 6.7.1.2, and 6.7.2.2.3, updated to provide clarification regarding dose modifications, with specifics on decoupling of magrolimab/placebo and azacitidine dosing. Section 8, updated to included updated sample size determination, interim analyses, endpoint definitions, efficacy analyses, safety analyses, extent of exposure, laboratory analyses. Section 9.5, updated to specify that birth year was collected, rather than date of birth. Appendices D, E, and F were updated to remove the text of the PRO instruments and provide a link to the instrument online, to avoid copyright infringement. Appendix I, updated to update the guidance regarding dosing delays of magrolimab. Additional minor changes have been made to improve clarity and consistency.
01 April 2022	In Amendment 6, Protocol 5F9009 updated to incorporate suggested changes to the protocol based on an Urgent Safety Measure communication. The primary reason for this amendment is to provide additional guidance for enhanced anemia management. Anemia is a known and well-described risk for magrolimab, which can occur in early doses and is transient. Adequate monitoring and management of anemia during the first 2 doses of magrolimab are needed to ensure participant safety, especially in participants with low baseline hemoglobin. A minimum hemoglobin threshold prior to the first 2 doses of magrolimab/placebo infusion along with hemoglobin monitoring after those magrolimab treatments are included in the amended protocol.

27 July 2022	In Amendment 7, the following has been amended: Objectives and Endpoints (Section 3), and associated text (DMC Interim Analysis Section 8.3.1, Table 18; Endpoint Definitions Section 8.4) was updated to re-order existing endpoints and add new secondary and exploratory endpoints for analysis; accordingly, endpoint language was also changed in Section 8.5.2. Table 3 and 4 (Schedule of Assessment), Footnote b was removed from the Vital Signs line entry. Extent and Maintenance of Blinding (Section 6.8.3) was updated to include a bullet point related to the blinding status of the vendors performing antidrug antibody- and pharmacokinetic-related data merging and analysis. A clarification was made to Worsening of Disease (Section 7.2.6) with regard to AE reporting. Pregnancy (Section 7.6) was updated to indicate that the Investigator must report any pregnancy occurring within 6 months of the last dose of study drug to the Sponsor within 24 hours of becoming aware of it. In Analysis Sets (Section 8.2), the definitions of the PK Analysis Set and the Immunogenicity Analysis Set were updated to state that they comprise all randomized participants "who received at least 1 dose of experimental drug". In Safety Analysis (Section 8.6), a clarification was made to the time period of the safety data. Appendix A (Azacitidine Prescribing Information) was removed. Appendix H (Section 13), contraception requirements for female participants, was updated. Appendix H (Section 13), procedures to be followed in the event of pregnancy, was updated. Additional changes to the protocol include the following: Schedule of Assessments (Section 4.3, Table 6) was updated to delete column specifying assessments for Days 29 to 57, as it was previously added in error. Footnote 'g' was also updated for clarification. Dosing and Administration (Section 6.4) was updated for clarification and to reduce redundancy.
11 October 2022	In Amendment 8, Protocol 5F9009 has been updated to clarify current language that does not specifically include the use of publicly available records as part of survival data in the case of withdrawal of consent. The major updates to the protocol and related rationale are as follows: Sections 4 and 5.7: Text is clarified to explicitly include withdrawal of consent as a circumstance in which sites may use public records in order to obtain information about survival status. Section 5.7.2: Text is removed that limits data analysis to data collected up until withdrawal of consent, in order to allow analysis of survival data collected from the search of public records. Additional changes to the protocol include the correction of typographical and formatting errors, where appropriate.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 January 2022	Food and Drug Administration (FDA) Division of Hematologic Malignancies I issued a partial clinical hold on studies evaluating magrolimab in combination with azacitidine in myelodysplastic syndromes and acute myeloid leukemia due to an apparent imbalance in investigator reported suspected unexpected serious adverse reactions (SUSARs). After comprehensive review of safety data, this hold was lifted on 11 Apr 2022 without further modification of safety language and no new safety signals were identified.	11 April 2022

18 July 2023	The DMC reviewed the results from the 2 planned interim efficacy analyses. Based on the prespecified superiority and futility rules, the DMC made recommendations to Gilead on whether the study should be stopped early due to overwhelming efficacy, be terminated for futility, or continue as planned.	-

Notes:

Limitations and caveats

None reported