



Clinical trial results:

A Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/ITD AML Summary

EudraCT number	2016-001061-83
Trial protocol	DE GB ES BE PL DK FR GR IT
Global end of trial date	09 May 2023

Results information

Result version number	v2 (current)
This version publication date	10 November 2024
First version publication date	09 May 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	2215-cl-0304
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02997202
WHO universal trial number (UTN)	-
Other trial identifiers	Bone and Marrow Transplant Clinical Trials Network: BMT-CTN 1506

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc
Sponsor organisation address	1 Astellas Way Northbrook, Illinois, United States, 60062
Public contact	Clinical Transparency, Astellas Pharma Global Development, Inc. (APGD), +1 8008887704, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Transparency, Astellas Pharma Global Development, Inc, +1 8008887704, astellas.resultsdisclosure@astellas.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	09 May 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare relapse free survival (RFS) between participants with FMS-like tyrosine kinase 3/Internal tandem duplication (FLT3/ITD) acute myeloid leukemia (AML) in first morphologic complete remission (CR1) who underwent hematopoietic stem cell transplantation (HSCT) and were randomized to receive gilteritinib or placebo beginning after the time of engraftment for a 2-year period.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 August 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	69 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Japan: 57
Country: Number of subjects enrolled	Korea, Republic of: 29
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 12

Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 152
Worldwide total number of subjects	356
EEA total number of subjects	68

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)	299
From 65 to 84 years	57
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with FLT3/ITD AML in first morphological CR1 including complete remission with incomplete platelet recovery (CRp) & complete remission with incomplete hematologic recovery (CRi) undergoing allogeneic hematopoietic cell transplant (HCT) were enrolled in the study.

Pre-assignment

Screening details:

Randomization was stratified by: Conditioning regimen intensity myeloablative vs reduced intensity/non-myeloablative (RIC/NMA); Time from first day of hematopoietic cell infusion to randomization (30 to 60 vs 61 to 90 days); Presence vs absence of/unknown, Minimal Residual Disease-4 (MRD-4) from the most recent pre-registration Bone marrow (BM).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gilteritinib

Arm description:

Participants received gilteritinib 120 milligrams (mg) (three tablets of 40 mg) orally, once daily (QD) for up to 2 years or until a protocol-defined discontinuation criterion was met.

Arm type	Experimental
Investigational medicinal product name	Gilteritinib
Investigational medicinal product code	ASP2215
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received gilteritinib 120 mg (three tablets of 40 mg) orally

Arm title	Placebo
------------------	---------

Arm description:

Participants received gilteritinib matching placebo orally, QD for up to 2 years or until a protocol-defined discontinuation criterion was met.

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

Dosage and administration details:

Participants received gilteritinib matching placebo orally

Number of subjects in period 1	Gilteritinib	Placebo
Started	178	178
Safety Analysis population	178	177
ITT Population	178	178
Completed	94	96
Not completed	84	82
Consent withdrawn by subject	14	17
Physician decision	5	3
Disease Relapse	15	41
Adverse event, non-fatal	31	10
Protocol Deviation	1	1
Graft Vs Host Disease (GVHD)	5	7
Death	8	2
Lost to follow-up	1	-
Non Compliance with study drug	3	1
Infection	1	-

Baseline characteristics

Reporting groups

Reporting group title	Gilteritinib
-----------------------	--------------

Reporting group description:

Participants received gilteritinib 120 milligrams (mg) (three tablets of 40 mg) orally, once daily (QD) for up to 2 years or until a protocol-defined discontinuation criterion was met.

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

Reporting group description:

Participants received gilteritinib matching placebo orally, QD for up to 2 years or until a protocol-defined discontinuation criterion was met.

Reporting group values	Gilteritinib	Placebo	Total
Number of subjects	178	178	356
Age categorical			
Units: participants			

Age			
Units: years			
arithmetic mean	50.3	51.8	
standard deviation	± 13.6	± 12.3	-
Sex			
Units: Participants			
Female	87	86	173
Male	91	92	183
Number of participants with conditioning regimen intensity			
Number of participants with conditioning regimen intensity categorized by myeloablative conditioning (MAC) vs RIC/NMA was reported. MAC regimen consisted: Total body irradiation (TBI) ≥ 5 gray (Gy) single dose or ≥ 8 Gy fractionated/oral Busulfan > 8 milligrams per kilogram (mg/kg)/6.4 mg/kg intravenous (IV) (total dose)/treosulfan >30000 milligrams per square meter (mg/m ²)/elphalan >150 mg/m ² /thiotepa ≥10 mg/kg. RIC/NMA: Any regimen that did not meet MAC regimen criteria. Interactive Response Technology (IRT) analysis was used.			
Units: Subjects			
MAC	103	103	206
RIC/NMA	75	75	150
Race			
Units: Subjects			
ASIAN	47	56	103
BLACK OR AFRICAN AMERICAN	6	3	9
UNKNOWN	11	13	24
WHITE	114	106	220
Ethnicity			
Units: Subjects			
HISPANIC OR LATINO	3	9	12
NOT HISPANIC OR LATINO	162	162	324
UNKNOWN	13	7	20
Presence of MRD			
Number of participants with presence versus absence of, or unknown, MRD-4 from the most recent pre-registration BM aspirate was reported. IRT analysis was used. The presence of MRD was considered "Detectable" if log10-transformed overall FLT3/ITD mutation ratio was greater than -4; otherwise, the presence of MRD was considered "Not Detectable."			

Units: Subjects			
Absent/Unknown	144	145	289
Present	34	33	67
Number of Participants With Time from first day of hematopoietic cell infusion to randomization			
Number of participants with time from first day of hematopoietic cell infusion to randomization categorized as 30 to 60 days vs 61 to 90 days were reported.			
Units: Subjects			
30-60 days	95	97	192
61-90 days	83	81	164

End points

End points reporting groups

Reporting group title	Gilteritinib
Reporting group description: Participants received gilteritinib 120 milligrams (mg) (three tablets of 40 mg) orally, once daily (QD) for up to 2 years or until a protocol-defined discontinuation criterion was met.	
Reporting group title	Placebo
Reporting group description: Participants received gilteritinib matching placebo orally, QD for up to 2 years or until a protocol-defined discontinuation criterion was met.	

Primary: Relapse-free survival (RFS)

End point title	Relapse-free survival (RFS)
End point description: RFS was defined as the time from the date of randomization until the date of documented morphological relapse, or death from any cause, whichever occurred first. Morphological relapse was defined as documentation of any of the following events: <ul style="list-style-type: none">• BM blasts \geq 5% (not attributable to regenerating BM)• Any circulating blasts (not attributable to regenerating BM or growth factors)• Presence of extramedullary blast foci per Revised International Working Group (RIWG) criteria• The earliest date of any of the relapse event were used for RFS. Intention-to-Treat (ITT) population: All randomized participants were included in this population. Here "99999" indicated that data was not estimable because less than 50% of participants had event (data was estimated using Kaplan-Meier [KM] and it requires at least 50% of event to be able to calculate time using KM).	
End point type	Primary
End point timeframe: From the date of randomization up to 64 months and 22 days	

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.0518
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.679
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.459
upper limit	1.005

Notes:

[1] - Stratification factors were conditioning regimen intensity MAC vs RIC/NMA, time from transplant to randomization (30 to 60 days vs 61 to 90 days), and the presence of MRD (present vs absent/unknown) based on the pre-transplant BM aspirate.

Secondary: Overall Survival (OS)

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

End point description:

OS was defined as the time from randomization until the date of death from any cause (death date – first dose date + 1). For a participant who was not known to have died by the end of study follow-up, OS was censored at the date of last contact (date of last contact – first dose date + 1).

ITT population.

Here “99999” indicated that data was not estimable because less than 50% of participants had event (data was estimated using KM and it requires at least 50% of event to be able to calculate time using KM).

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

End point timeframe:

From the date of randomization until 65 months

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.4394
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.554
upper limit	1.293

Notes:

[2] - Stratification factors were conditioning regimen intensity MAC vs RIC/NMA, time from transplant to randomization (30 to 60 days vs 61 to 90 days), and the presence of MRD (present vs absent/unknown) based on the pre-transplant BM aspirate.

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

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

End point description:

An Adverse event (AE) was any untoward medical occurrence in a participant administered a study drug, and which did not have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

TEAE defined as an AE event observed through 30 days after the last dose.

Safety Analysis Population: consisted of all participants who took at least 1 dose of study drug (gilteritinib or placebo).

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

End point timeframe:

From the date of randomization through 30 days after the last dose, up to 25 months and 22 days

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	177		
Units: participants	175	162		

Statistical analyses

No statistical analyses for this end point

Secondary: Karnofsky Performance Status Scores

End point title	Karnofsky Performance Status Scores
-----------------	-------------------------------------

End point description:

KPS scores of participants were reported. KPS was a standard way of measuring ability of cancer participants to perform ordinary tasks. It was 11 level score which ranged between 0-100%. 100 =Normal, no complaints, no evidence of disease 90 =Able to carry on normal activity, minor signs or symptoms of disease 80 =Normal activity with effort, some signs or symptoms of disease 70 =Care for

self, unable to carry on normal activity or to do work 60 =Required occasional assistance but was able to care for most of his needs 50 =Required considerable assistance & frequent medical care 40 =Disabled, required special care & assistance 30 = Severely disabled, hospitalization indicated, although death not imminent 20 =Very sick, hospitalization necessary, active supportive treatment necessary 10 =moribund fatal processes progressing rapidly 0 =Dead. Safety Analysis Population with available data was analyzed.

End point type	Secondary
End point timeframe:	
Baseline, month 24	

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	169		
Units: unit on a scale				
arithmetic mean (standard deviation)				
Baseline (N =174, 169)	84.20 (± 10.65)	84.73 (± 10.69)		
Month 24 (N =93, 96)	93.12 (± 8.34)	91.67 (± 9.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Non-relapse Mortality (NRM)

End point title	Percentage of Participants with Non-relapse Mortality (NRM)
-----------------	-------------------------------------------------------------

End point description:

NRM was defined as death from any cause other than relapse or disease progression (DP). Relapse was defined as documentation of any of the following events:

- BM blasts ≥ 5% (not attributable to regenerating BM)
- Any circulating blasts (not attributable to regenerating BM or growth factors)
- Presence of extramedullary blast foci per RIWG criteria
- The earliest date of any of the relapse event were used for RFS.

DP: ≥20% increase in sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline, sum must also be absolute increase of ≥5 mm. Unequivocal progression of existing non-target lesions. Appearance of at least 1 new lesion. Incidence of NRM was estimated using the cumulative incidence function, treating relapse/progression as a competing risk.

ITT population

End point type	Secondary
End point timeframe:	
From the date of randomization up to 64 months and 22 days	

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: percentage of participants				
number (confidence interval 95%)	13.6 (8.9 to 19.2)	6.6 (3.5 to 11.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.0209
Method	Fine-Grays Model
Parameter estimate	Hazard ratio (HR)
Point estimate	2.308
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1352
upper limit	4.6922

Notes:

[3] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days) and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Secondary: Event-free Survival (EFS)

End point title	Event-free Survival (EFS)
End point description:	EFS: Time from date of randomization until documented relapse, or premature discontinuation of treatment or initiation of other anti-leukemic treatment or death from any cause, whichever occurred first. Relapse was defined as documentation of any of following events: • BM blasts \geq 5% (not attributable to regenerating BM) • Any circulating blasts (not attributable to regenerating BM or growth factors) • Presence of extramedullary blast foci per RIWG criteria • The earliest date of any of relapse event were used for RFS. Anti-leukemic treatment was defined as hypomethylating agents, chemotherapy, oral anticancer agents, Donor lymphocyte infusion (DLI) or cellular therapies given because of detectable disease, not meeting R-IWG criteria for relapse. ITT population. Here "99999" indicated that data was not estimable because less than 50% of participants had event (data was estimated using KM and it requires at least 50% of event to be able to calculate time using KM).
End point type	Secondary
End point timeframe:	From the date of randomization until 65 months

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: months				
median (confidence interval 95%)	99999 (19.65 to 99999)	99999 (15.05 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.6417 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.686
upper limit	1.261

Notes:

[4] - Stratification factors were conditioning regimen intensity MAC vs RIC/NMA, time from transplant to randomization (30 to 60 days vs 61 to 90 days), and the presence of MRD (present vs absent/unknown) based on the pre-transplant BM aspirate.

[5] - Stratification factors were conditioning regimen intensity MAC vs RIC/NMA, time from transplant to randomization (30 to 60 days vs 61 to 90 days), and the presence of MRD (present vs absent/unknown) based on the pre-transplant BM aspirate.

Secondary: Percentage of Participants with Treatment Emergent Acute Graft vs. Host Disease (aGVHD)

End point title	Percentage of Participants with Treatment Emergent Acute Graft vs. Host Disease (aGVHD)
-----------------	-----------------------------------------------------------------------------------------

End point description:

The cumulative incidence at 6 months after randomization of grades II-IV and grades III-IV aGVHD were reported, treating death prior to aGVHD as the competing risk. It was graded according to diagnosis and severity scoring used by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The acute GVHD algorithm calculated the grade based on the organ (skin, gastrointestinal (GI) and liver) stage and etiology/biopsy reported on the weekly GVHD form. Grade I aGVHD was defined as Skin stage of 1-2 and stage 0 for both GI and liver organs. Grade II aGVHD was stage 3 of skin, or stage 1 of GI, or stage 1 of liver. Grade III is stage 2-4 for GI, or stage 2-3 of liver. Grade IV was stage 4 of skin, or stage 4 of liver. Grade IV was the worst outcome. Treatment emergent was defined as an event observed through 30 days after the last dose

ITT population

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

End point timeframe:

From the date of randomization up to 6 months

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: percentage of participants				
arithmetic mean (confidence interval 95%)				
aGVHD II to IV	16.5 (11.3 to 22.5)	19.2 (13.6 to 25.6)		
aGVHD III to IV	5.9 (3.0 to 10.1)	4.1 (1.8 to 7.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2 (aGVHD III to IV)
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.4128
Method	Fine-Grays model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4254
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6103
upper limit	3.3289

Notes:

[6] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days) and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Statistical analysis title	Statistical Analysis 1 (aGVHD II to IV)
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.641
Method	Fine-Grays model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8938
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5574
upper limit	1.433

Notes:

[7] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days) and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Secondary: Percentage of Participants with Treatment Emergent Chronic GVHD at 12 months

End point title	Percentage of Participants with Treatment Emergent Chronic GVHD at 12 months
-----------------	------------------------------------------------------------------------------

End point description:

Chronic GVHD was graded according to diagnosis and severity scoring from the National Institute of Health (NIH) 2014 Consensus Criteria. Eight organs - skin, mouth, liver, upper and lower gastrointestinal, esophagus, lung, eye, and joint/fascia were scored on a 0-3 scale to reflect degree of chronic GVHD involvement, where 0 = no involvement/no symptoms & 3 indicated the worst symptom. This system staged severity in each individual organ, and then a global score defined as mild, moderate or severe, based on number of organs involved and organ severity score was calculated. The cumulative incidence of chronic GVHD (mild, moderate, severe) at 12 months after randomization was reported, treating death prior to chronic GVHD as the competing risk. Treatment emergent was defined as an event observed through 30 days after the last dose.

ITT population

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

End point timeframe:

From the date of randomization up to 12 months

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: percentage of participants				
number (confidence interval 95%)	57.0 (48.5 to 64.6)	48.1 (39.5 to 56.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[8]
P-value	= 0.1725
Method	Fine-Grays Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.236
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9116
upper limit	1.6757

Notes:

[8] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days) and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Secondary: Percentage of Participants with Treatment Emergent Chronic GVHD at 24 months

End point title	Percentage of Participants with Treatment Emergent Chronic GVHD at 24 months
-----------------	------------------------------------------------------------------------------

End point description:

Chronic GVHD was graded according to diagnosis and severity scoring from the NIH 2014 Consensus Criteria. Eight organs- skin, mouth, liver, upper and lower gastrointestinal, esophagus, lung, eye, and joint/fascia are scored on a 0-3 scale to reflect degree of chronic GVHD involvement where 0 = no involvement/no symptoms & 3 indicated the worst symptom. This system staged severity in each individual organ, and then a global score defined as mild, moderate or severe, based on number of organs involved and organ severity score was calculated. The cumulative incidence of chronic GVHD (mild, moderate, severe) at 24 months after randomization was reported, treating death prior to chronic GVHD as the competing risk. Treatment emergent was defined as an event observed through 30 days after the last dose.

ITT population

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

End point timeframe:

From the date of randomization up to 24 months

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: percentage of participants				
number (confidence interval 95%)	61.9 (53.3 to 69.4)	51.8 (42.9 to 59.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.1725
Method	Fine-Grays Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.236
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9116
upper limit	1.6757

Notes:

[9] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days) and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Secondary: Percentage of Participants with FMS-like tyrosine kinase 3/Internal tandem duplication (FLT3/ITD) Minimal residual disease (MRD)

End point title	Percentage of Participants with FMS-like tyrosine kinase 3/Internal tandem duplication (FLT3/ITD) Minimal residual disease (MRD)
-----------------	----------------------------------------------------------------------------------------------------------------------------------

End point description:

The presence of MRD was considered Detectable in participants who were FLT3/ITD MRD undetectable prior to randomization if log10-transformed overall FLT3/ITD mutation ratio greater than -4 otherwise presence of MRD was considered Not Detectable. Participants who had detectable FLT3/ITD MRD prior to randomization were considered eradicated if log10-transformed overall FLT3/ITD mutation ratio \leq -4. Incidence of MRD Eradication and Detection were estimated using the cumulative incidence function, treating death during MRD assessment period without documentation of MRD event as competing risk. ITT population with available data was analyzed.

Here 99999 indicated data not estimable because no participants in Placebo group were followed up to 1 year (cumulative incidence function requires at least 1 participant to calculate the cumulative incidence rate).

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

End point timeframe:

From the date of randomization up to 64 months and 22 days

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	165	162		
Units: percentage of participants				
number (confidence interval 95%)				
MRD Eradication (N =8,10)	80.0 (4.7 to 98.4)	99999 (99999 to 99999)		
MRD 10^{-4} Detection (N =165,162)	7.1 (3.4 to 12.4)	9.2 (5.0 to 15.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2 (MRD 10^{-4} Detection)
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4077
Method	Fine-Grays Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3116
upper limit	1.6055

Statistical analysis title	Statistical Analysis 1 (MRD Eradication)
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2029
Method	Fine-Grays Model
Parameter estimate	Hazard ratio (HR)
Point estimate	3.4537
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5126
upper limit	23.2687

Secondary: Percentage of Participants with Relapse

End point title	Percentage of Participants with Relapse
End point description:	
Cumulative incidence of relapse was reported, treating death in remission as a competing risk. Relapse was defined as documentation of any of the following events:	
<ul style="list-style-type: none"> • BM blasts \geq 5% (not attributable to regenerating BM) • Any circulating blasts (not attributable to regenerating BM or growth factors) • Presence of extramedullary blast foci per RIWG criteria • The earliest date of any of the relapse event were used for RFS. 	
ITT population	
End point type	Secondary
End point timeframe:	
From the date of randomization up to 64 months and 22 days	

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: percentage of participants				
number (confidence interval 95%)	12.4 (7.9 to 17.8)	26.7 (20.3 to 33.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	< 0.001
Method	Fine-Grays Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3729
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2243
upper limit	0.6199

Notes:

[10] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days), and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Secondary: Percentage of Participants with Treatment Emergent Infection by Severity

End point title	Percentage of Participants with Treatment Emergent Infection by Severity
-----------------	--------------------------------------------------------------------------

End point description:

Severity of Infection was assessed based on the following criteria:

Grade 1-Mild Asymptomatic or mild symptoms, clinical or diagnostic observations noted intervention not indicated.

Grade 2-Moderate Local or noninvasive intervention indicated.

Grade 3-Severe Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.

Grade 4-Life Threatening Life threatening consequences, urgent intervention indicated.

Grade 5-Death related to the AE. Cumulative incidence of grade 3 to 5 infections were reported, treating death (grade 5) as a competing event. Treatment emergent was defined as an event observed through 30 days after the last dose.

ITT population

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

End point timeframe:

From the date of randomization through 30 days after the last dose, up to 25 months and 22 days

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	178		
Units: percentage of participants				
number (confidence interval 95%)	39.6 (31.3 to 47.8)	27.2 (19.9 to 35.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo

Number of subjects included in analysis	356
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.0568
Method	Fine-Grays model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.4848
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9886
upper limit	2.23

Notes:

[11] - Based on Fine and Gray's model adjusting for conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days), and the presence of MRD (present vs absent/indeterminate) based on the pre-transplant BM aspirate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From the date of randomization up to 64 months and 22 days

Adverse events: From the date of randomization through 30 days after the last dose, up to 25 months and 22 days

Adverse event reporting additional description:

Safety Analysis Population. All-cause mortality, serious & other adverse events were reported for all randomized participants who received actual dose of study drug during study. 1 participant randomized to placebo received gilteritinib, was included under gilteritinib arm. 1 participant randomized to gilteritinib arm did not receive any treatment.

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

Dictionary used

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

Dictionary version	v23
--------------------	-----

Reporting groups

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

Reporting group description:

Participants received to gilteritinib matching placebo orally, QD for up to 2 years or until a protocol-defined discontinuation criterion was met.

Reporting group title	Gilteritinib
-----------------------	--------------

Reporting group description:

Participants received gilteritinib 120 mg (three tablets of 40 mg) orally, QD for up to 2 years or until a protocol-defined discontinuation criterion was met.

Serious adverse events	Placebo	Gilteritinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 177 (45.76%)	92 / 178 (51.69%)	
number of deaths (all causes)	44	42	
number of deaths resulting from adverse events	9	12	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	5 / 177 (2.82%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratoacanthoma			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large granular lymphocytosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemic retinopathy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal squamous cell carcinoma			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post transplant lymphoproliferative disorder			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vena cava thrombosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Unintended pregnancy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (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			
Pyrexia			
subjects affected / exposed	4 / 177 (2.26%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyserositis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	22 / 177 (12.43%)	19 / 178 (10.67%)	
occurrences causally related to treatment / all	1 / 27	0 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute graft versus host disease in liver			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic graft versus host disease			
subjects affected / exposed	8 / 177 (4.52%)	10 / 178 (5.62%)	
occurrences causally related to treatment / all	0 / 8	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in lung			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Reproductive system and breast disorders			
Vulvovaginal adhesion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 177 (1.69%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Somatic symptom disorder			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 177 (0.00%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	2 / 177 (1.13%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect dose administered			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medication error			
subjects affected / exposed	6 / 177 (3.39%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	2 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antithrombin III deficiency			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 177 (1.13%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Atrial fibrillation			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prinzmetal angina			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor neurone disease			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis transverse			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytopenia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 177 (1.13%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	0 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 177 (0.56%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deafness			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
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	2 / 177 (1.13%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 177 (2.26%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	1 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal impairment			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
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			
Muscular weakness			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyositis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	6 / 177 (3.39%)	16 / 178 (8.99%)	
occurrences causally related to treatment / all	2 / 7	4 / 20	
deaths causally related to treatment / all	0 / 0	2 / 3	
Pharyngeal abscess			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 177 (0.56%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis bacterial			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Central nervous system infection			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
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 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 177 (0.56%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pseudomembranous colitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 177 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral haemorrhagic cystitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 177 (0.00%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoviral upper respiratory infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 177 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus enterocolitis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter sepsis			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epstein-Barr viraemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			

subjects affected / exposed	2 / 177 (1.13%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenovirus infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
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 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	3 / 177 (1.69%)	6 / 178 (3.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 177 (1.13%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			

subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	2 / 177 (1.13%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (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 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	0 / 177 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonas infection			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital infection bacterial			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection fungal			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 177 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			

subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 177 (0.00%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	0 / 177 (0.00%)	3 / 178 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Viral skin infection			
subjects affected / exposed	1 / 177 (0.56%)	0 / 178 (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 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 177 (0.00%)	1 / 178 (0.56%)	
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 / 177 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 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	Gilteritinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 177 (95.48%)	175 / 178 (98.31%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 177 (7.34%)	28 / 178 (15.73%)	
occurrences (all)	21	35	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 177 (15.82%)	30 / 178 (16.85%)	
occurrences (all)	29	40	
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	1 / 177 (0.56%) 1	10 / 178 (5.62%) 11	
Oedema peripheral subjects affected / exposed occurrences (all)	22 / 177 (12.43%) 27	28 / 178 (15.73%) 30	
Pyrexia subjects affected / exposed occurrences (all)	16 / 177 (9.04%) 20	16 / 178 (8.99%) 20	
Immune system disorders Chronic graft versus host disease subjects affected / exposed occurrences (all)	77 / 177 (43.50%) 131	94 / 178 (52.81%) 156	
Acute graft versus host disease subjects affected / exposed occurrences (all)	64 / 177 (36.16%) 91	67 / 178 (37.64%) 90	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	30 / 177 (16.95%) 39	33 / 178 (18.54%) 40	
Dyspnoea subjects affected / exposed occurrences (all)	13 / 177 (7.34%) 15	17 / 178 (9.55%) 21	
Oropharyngeal pain subjects affected / exposed occurrences (all)	9 / 177 (5.08%) 11	11 / 178 (6.18%) 12	
Rhinorrhoea subjects affected / exposed occurrences (all)	9 / 177 (5.08%) 13	4 / 178 (2.25%) 4	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 4	10 / 178 (5.62%) 10	
Insomnia subjects affected / exposed occurrences (all)	17 / 177 (9.60%) 19	14 / 178 (7.87%) 15	
Investigations			

White blood cell count decreased subjects affected / exposed occurrences (all)	8 / 177 (4.52%) 8	22 / 178 (12.36%) 31	
Platelet count decreased subjects affected / exposed occurrences (all)	17 / 177 (9.60%) 21	32 / 178 (17.98%) 44	
Neutrophil count decreased subjects affected / exposed occurrences (all)	17 / 177 (9.60%) 43	49 / 178 (27.53%) 64	
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 177 (0.00%) 0	9 / 178 (5.06%) 11	
Blood creatinine increased subjects affected / exposed occurrences (all)	12 / 177 (6.78%) 21	17 / 178 (9.55%) 22	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	3 / 177 (1.69%) 3	33 / 178 (18.54%) 41	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	13 / 177 (7.34%) 13	15 / 178 (8.43%) 18	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	21 / 177 (11.86%) 24	29 / 178 (16.29%) 40	
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	22 / 177 (12.43%) 26	33 / 178 (18.54%) 44	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	14 / 177 (7.91%) 15	24 / 178 (13.48%) 34	
Headache subjects affected / exposed occurrences (all)	13 / 177 (7.34%) 17	19 / 178 (10.67%) 23	
Paraesthesia			

subjects affected / exposed occurrences (all)	7 / 177 (3.95%) 7	9 / 178 (5.06%) 10	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	2 / 177 (1.13%) 2	9 / 178 (5.06%) 9	
Neuropathy peripheral subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 5	9 / 178 (5.06%) 10	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	20 / 177 (11.30%) 24	30 / 178 (16.85%) 36	
Neutropenia subjects affected / exposed occurrences (all)	11 / 177 (6.21%) 13	23 / 178 (12.92%) 30	
Thrombocytopenia subjects affected / exposed occurrences (all)	13 / 177 (7.34%) 14	22 / 178 (12.36%) 29	
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	21 / 177 (11.86%) 21	19 / 178 (10.67%) 21	
Gastrointestinal disorders			
Vomiting subjects affected / exposed occurrences (all)	28 / 177 (15.82%) 34	24 / 178 (13.48%) 34	
Dry mouth subjects affected / exposed occurrences (all)	15 / 177 (8.47%) 17	22 / 178 (12.36%) 26	
Diarrhoea subjects affected / exposed occurrences (all)	30 / 177 (16.95%) 48	44 / 178 (24.72%) 55	
Constipation subjects affected / exposed occurrences (all)	12 / 177 (6.78%) 14	20 / 178 (11.24%) 22	
Abdominal pain			

subjects affected / exposed	11 / 177 (6.21%)	11 / 178 (6.18%)	
occurrences (all)	13	13	
Nausea			
subjects affected / exposed	40 / 177 (22.60%)	38 / 178 (21.35%)	
occurrences (all)	47	48	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	7 / 177 (3.95%)	14 / 178 (7.87%)	
occurrences (all)	7	16	
Pruritus			
subjects affected / exposed	13 / 177 (7.34%)	13 / 178 (7.30%)	
occurrences (all)	15	13	
Rash			
subjects affected / exposed	16 / 177 (9.04%)	10 / 178 (5.62%)	
occurrences (all)	22	13	
Rash maculo-papular			
subjects affected / exposed	9 / 177 (5.08%)	12 / 178 (6.74%)	
occurrences (all)	11	13	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 177 (3.39%)	15 / 178 (8.43%)	
occurrences (all)	6	17	
Myalgia			
subjects affected / exposed	9 / 177 (5.08%)	18 / 178 (10.11%)	
occurrences (all)	13	19	
Muscle spasms			
subjects affected / exposed	6 / 177 (3.39%)	13 / 178 (7.30%)	
occurrences (all)	6	13	
Back pain			
subjects affected / exposed	8 / 177 (4.52%)	16 / 178 (8.99%)	
occurrences (all)	9	19	
Arthralgia			
subjects affected / exposed	12 / 177 (6.78%)	14 / 178 (7.87%)	
occurrences (all)	13	15	
Infections and infestations			

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	11 / 177 (6.21%) 11	18 / 178 (10.11%) 21	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	22 / 177 (12.43%) 34	21 / 178 (11.80%) 25	
Pneumonia subjects affected / exposed occurrences (all)	10 / 177 (5.65%) 12	8 / 178 (4.49%) 9	
Influenza subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 5	11 / 178 (6.18%) 11	
Cytomegalovirus viraemia subjects affected / exposed occurrences (all)	12 / 177 (6.78%) 16	8 / 178 (4.49%) 10	
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	4 / 177 (2.26%) 8	17 / 178 (9.55%) 23	
Hypomagnesaemia subjects affected / exposed occurrences (all)	12 / 177 (6.78%) 25	13 / 178 (7.30%) 17	
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 177 (1.13%) 2	9 / 178 (5.06%) 10	
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 177 (1.69%) 3	13 / 178 (7.30%) 15	
Decreased appetite subjects affected / exposed occurrences (all)	18 / 177 (10.17%) 26	11 / 178 (6.18%) 12	
Hypophosphataemia subjects affected / exposed occurrences (all)	5 / 177 (2.82%) 6	9 / 178 (5.06%) 14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2017	<ul style="list-style-type: none">Administrative and grammatical changes, updated for clarity and consistency throughout the protocol.
15 March 2019	<ul style="list-style-type: none">Modification of Registration Inclusion Laboratory Results Criteria. Criterion #7d, which is related to serum and potassium lower limits of normal, has been removed from the registration inclusion criteria section.Revise Laboratory Value Language. The randomization criteria language for serum potassium and magnesium laboratory values (criterion "D") has been revised to include "or equal to" the institutional lower limit of normal (LLN).Clarification of Timing of Treatment Administration. The time of drug administration was clarified to indicate that drug should be taken in the morning.Revision of Unblinding Language. Language has been added to clarify the conditions under which unblinding could occur, including in the event of documented relapse.Modification of Pregnancy Testing Evaluation. The word "monthly" has been removed from item number 7 in the "Evaluations during Treatment" section.Addition of Text to Analysis of Secondary Endpoints. The secondary endpoint analysis section is updated with text indicating that additional analyses will be performed to assess the impact of crossover after unblinding on overall survival.
19 August 2022	<ul style="list-style-type: none">Change in timing of primary analysisAddition of power calculation for 2.5 years after last participant was randomizedThe secondary objective of OS is changed to a key secondary objective, and the description of timing for the OS analyses is updated.80% of RFS events have occurred is removed from the Criteria for Removal from Study.Updates made to the sensitivity analyses for the primary endpoint analysis of RFS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported