



## Clinical trial results:

### A Phase 3 Open-Label, Multicenter, Randomized Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) with FLT3 Mutation

#### Summary

EudraCT number	2015-000140-42
Trial protocol	DE GB BE ES IE FR PL IT
Global end of trial date	25 February 2025

#### Results information

Result version number	v1 (current)
This version publication date	05 September 2025
First version publication date	05 September 2025

#### Trial information

##### Trial identification

Sponsor protocol code	2215-CL-0301
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02421939
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc.
Sponsor organisation address	1 Astellas Way, Northbrook, United States, 60062
Public contact	Clinical Transparency, Astellas Pharma Global Development, Inc., +1 800-888-770, <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a>
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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	25 February 2025
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 February 2025
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to determine the clinical benefit of ASP2215 therapy in participants with FMS-like tyrosine kinase (FLT3) mutated acute myeloid leukemia (AML) who were refractory to or had relapsed after first-line AML therapy as shown with overall survival (OS) compared to salvage chemotherapy, and determined the efficacy of ASP2215 therapy as assessed by the rate of complete remission and complete remission with partial hematological recovery (CR/CRh) in these participants. This study also determined the overall efficacy in event-free survival (EFS) and complete remission (CR) rate of ASP2215 compared to salvage chemotherapy.

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	20 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 33
Country: Number of subjects enrolled	Japan: 48
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Türkiye: 1

Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 162
Worldwide total number of subjects	371
EEA total number of subjects	97

Notes:

<b>Subjects enrolled per age group</b>	
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)	216
From 65 to 84 years	154
85 years and over	1

## Subject disposition

### Recruitment

#### Recruitment details:

Participants were recruited from approximately 140 centers in North America, Europe, Asia and the rest of the world and randomized in a 2:1 ratio to receive gilteritinib or salvage chemotherapy. Participants had FMS-like tyrosine kinase 3 (FLT3) mutations and relapsed or refractory acute myeloid leukemia (AML) after first-line therapy.

### Pre-assignment

#### Screening details:

Participants entered the screening period up to 14 days prior to the start of treatment. Prior to randomization, the investigator preselected a salvage chemotherapy for each participant. The randomization was stratified by response to first-line AML therapy and preselected salvage chemotherapy. Treatment was given over continuous 28-day cycles.

### Period 1

Period 1 title	Randomization Period: Up to 3 years
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
Arm title	Gilteritinib

#### Arm description:

Participants received 120 mg dose (3 tablets of 40 mg) orally once a day in continuous 28-day cycles, at least 2 hours after or 1 hour before food. Gilteritinib treatment continued until participants met one of the treatment discontinuation criteria. After the end of treatment period, participants were allowed to enter long-term follow up period for up to 3 years for collection of subsequent AML treatment, EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L), remission status and survival (cause of death and date of death). Participants continuing to derive clinical benefit from gilteritinib as assessed by the investigator were allowed to continue the study treatment until a discontinuation criterion was met or if they had completed more than 3 years of treatment.

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

#### Dosage and administration details:

120mg tablet orally once a day

Arm title	Salvage Chemotherapy
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#### Arm description:

Participants received chemotherapy in 28-day cycles. Low-Dose Cytarabine (LoDAC): 20 mg of cytarabine twice daily by subcutaneous (SC)/intravenous (IV) injection for 10 days. Participants on azacitidine: 75 mg/m<sup>2</sup> daily by SC/IV injection for 7 days. Participants on LoDAC or azacitidine treatment continued until they met discontinuation criteria. MEC chemotherapy: mitoxantrone 8 mg/m<sup>2</sup> daily by IV for 5 days, etoposide 100 mg/m<sup>2</sup> daily by IV for 5 days and cytarabine 1000 mg/m<sup>2</sup> daily by IV for 5 days (days 1-5). FLAG-IDA chemotherapy: G-CSF 300 µg/m<sup>2</sup> daily by SC/IV for 5 days (days 1-5), fludarabine 30 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6), cytarabine 2000 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6) and idarubicin 10 mg/m<sup>2</sup> daily by IV for 3 days (days 2-4). MEC or FLAG-IDA: 1 cycle of therapy and were assessed on/after day 15. Participants were allowed to enter LTFU period of up to 3 years for collection of subsequent AML treatment, EQ-5D-5L, remission status and survival.

Arm type	Experimental
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Investigational medicinal product name	MEC (Mitoxantrone, Etoposide, Cytarabine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: Mitoxantrone: 8 mg/m <sup>2</sup> daily by IV Etoposide: 100mg/m <sup>2</sup> daily Cytarabine: 1000 mg/m <sup>2</sup> daily by IV	
Investigational medicinal product name	FLAG-IDA (Granulocyte-Colony Stimulating Factor (G-CSF), Fludarabine, Cytarabine, Idarubicin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use , Subcutaneous use
Dosage and administration details: G-CSF: 300 µg/m <sup>2</sup> daily by SC/IV Fludarabine: 30 mg/m <sup>2</sup> daily by IV Cytarabine: 2000 mg/m <sup>2</sup> daily by IV Idarubicin 10mg/m <sup>2</sup> daily by IV for 3 days.	
Investigational medicinal product name	LoDAC (Low Dose Cytarabine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use
Dosage and administration details: 20 mg of cytarabine twice daily by SC or IV injection	
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use
Dosage and administration details: 75 mg/m <sup>2</sup> daily by SC or IV injection	

<b>Number of subjects in period 1</b>	Gilteritinib	Salvage Chemotherapy
Started	247	124
Treated	246	109
Completed	0	19
Not completed	247	105
Adverse event, serious fatal	38	10
Physician decision	13	11
Consent withdrawn by subject	9	24
Adverse event, non-fatal	32	5
Protocol deviation	1	1
Miscellaneous	20	5
Disease relapse	37	2

Progressive disease	76	16
Lack of efficacy	21	31

## Period 2

Period 2 title	Long-term follow-up: up to 3 years
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	No
<b>Arm title</b>	Gilteritinib

### Arm description:

Participants received 120 mg dose (3 tablets of 40 mg) orally once a day in continuous 28-day cycles, at least 2 hours after or 1 hour before food. Gilteritinib treatment continued until participants met one of the treatment discontinuation criteria.

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

### Dosage and administration details:

120mg tablet orally once a day

<b>Arm title</b>	Salvage Chemotherapy
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### Arm description:

Participants received chemotherapy in 28-day cycles. Participants on Low-Dose Cytarabine (LoDAC) received 20 mg of cytarabine twice daily by subcutaneous (SC) or intravenous (IV) injection for 10 days. Participants on azacitidine received 75 mg/m<sup>2</sup> daily by SC or IV injection for 7 days. Participants on LoDAC or azacitidine treatment continued until they met discontinuation criteria. Participants on MEC chemotherapy received mitoxantrone 8 mg/m<sup>2</sup> daily by IV for 5 days, etoposide 100 mg/m<sup>2</sup> daily by IV for 5 days and cytarabine 1000 mg/m<sup>2</sup> daily by IV for 5 days (days 1-5). Participants on FLAG-IDA chemotherapy received G-CSF 300 µg/m<sup>2</sup> daily by SC/IV for 5 days (days 1-5), fludarabine 30 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6), cytarabine 2000 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6) and idarubicin 10 mg/m<sup>2</sup> daily by IV for 3 days (days 2-4). Participants receiving MEC or FLAG-IDA received 1 cycle of therapy and were assessed for response on or after day 15.

Arm type	Experimental
Investigational medicinal product name	MEC (Mitoxantrone, Etoposide, Cytarabine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

### Dosage and administration details:

Mitoxantrone: 8 mg/m<sup>2</sup> daily by IV  
Etoposide: 100mg/m<sup>2</sup> daily  
Cytarabine: 1000 mg/m<sup>2</sup> daily by IV

Investigational medicinal product name	FLAG-IDA (Granulocyte-Colony Stimulating Factor (G-CSF), Fludarabine, Cytarabine, Idarubicin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use , Subcutaneous use
Dosage and administration details: G-CSF: 300 µg/m <sup>2</sup> daily by SC/IV Fludarabine: 30 mg/m <sup>2</sup> daily by IV Cytarabine: 2000 mg/m <sup>2</sup> daily by IV Idarubicin 10mg/m <sup>2</sup> daily by IV for 3 days.	
Investigational medicinal product name	LoDAC (Low Dose Cytarabine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use
Dosage and administration details: 20 mg of cytarabine twice daily by SC or IV injection	
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use, Subcutaneous use
Dosage and administration details: 75 mg/m <sup>2</sup> daily by SC or IV injection	

<b>Number of subjects in period 2</b>	Gilteritinib	Salvage Chemotherapy
Started	133	73
Completed	0	0
Not completed	133	73
Adverse event, serious fatal	118	65
Consent withdrawn by subject	4	5
Miscellaneous	10	1
Lost to follow-up	1	2

## Baseline characteristics

### Reporting groups

Reporting group title	Gilteritinib
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Reporting group description:

Participants received 120 mg dose (3 tablets of 40 mg) orally once a day in continuous 28-day cycles, at least 2 hours after or 1 hour before food. Gilteritinib treatment continued until participants met one of the treatment discontinuation criteria. After the end of treatment period, participants were allowed to enter long-term follow up period for up to 3 years for collection of subsequent AML treatment, EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L), remission status and survival (cause of death and date of death). Participants continuing to derive clinical benefit from gilteritinib as assessed by the investigator were allowed to continue the study treatment until a discontinuation criterion was met or if they had completed more than 3 years of treatment.

Reporting group title	Salvage Chemotherapy
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Reporting group description:

Participants received chemotherapy in 28-day cycles. Low-Dose Cytarabine (LoDAC): 20 mg of cytarabine twice daily by subcutaneous (SC)/intravenous (IV) injection for 10 days. Participants on azacitidine: 75 mg/m<sup>2</sup> daily by SC/IV injection for 7 days. Participants on LoDAC or azacitidine treatment continued until they met discontinuation criteria. MEC chemotherapy: mitoxantrone 8 mg/m<sup>2</sup> daily by IV for 5 days, etoposide 100 mg/m<sup>2</sup> daily by IV for 5 days and cytarabine 1000 mg/m<sup>2</sup> daily by IV for 5 days (days 1-5). FLAG-IDA chemotherapy: G-CSF 300 µg/m<sup>2</sup> daily by SC/IV for 5 days (days 1-5), fludarabine 30 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6), cytarabine 2000 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6) and idarubicin 10 mg/m<sup>2</sup> daily by IV for 3 days (days 2-4). MEC or FLAG-IDA: 1 cycle of therapy and were assessed on/after day 15. Participants were allowed to enter LTFU period of up to 3 years for collection of subsequent AML treatment, EQ-5D-5L, remission status and survival.

Reporting group values	Gilteritinib	Salvage Chemotherapy	Total
Number of subjects	247	124	371
Age categorical Units: Subjects			

Age Units: years			
arithmetic mean	59	57.6	
standard deviation	± 14.6	± 14.8	-
Sex Units: Subjects			
Female	131	70	201
Male	116	54	170
Analysis Race Units: Subjects			
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
ASIAN	69	33	102
BLACK OR AFRICAN AMERICAN	14	7	21
MISSING	9	4	13
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	0	1
OTHER	5	1	6
UNKNOWN	4	4	8
WHITE	145	75	220
Ethnicity Units: Subjects			



HISPANIC OR LATINO	12	2	14
MISSING	11	4	15
NOT HISPANIC OR LATINO	221	116	337
UNKNOWN	3	2	5
Cytogenetic Risk Status			
The category of "Other" includes those with cytogenetic risk status that cannot be categorized as favorable, intermediate or unfavorable.			
Units: Subjects			
INTERMEDIATE	182	89	271
UNFAVORABLE	26	11	37
FAVORABLE	4	1	5
OTHER	35	23	58
Response to First Line Therapy- Preselected Salvage Chemotherapy			
Baseline stratification factors. HSCT is hematopoietic stem cell transplant. CRc is composite complete remission.			
Units: Subjects			
Primary refractory w/o HSCT, high intensity (IT)	57	28	85
Primary refractory w/o HSCT, low IT	41	20	61
Relapse w/I 6 mths after CRc and no HSCT, high IT	40	21	61
Relapse w/I 6 mths after CRc and no HSCT low IT	27	13	40
Relapse after 6 mths after CRc and no HSCT high IT	23	11	34
Relapse w/I 6 mths after allogeneic HSCT low IT	16	9	25
Relapse w/I 6 mths after allogeneic HSCT high IT	15	8	23
Relapse after 6 mths after allogeneic HSCT high IT	14	7	21
Relapse after 6 mths after CRc and no HSCT low IT	11	6	17
Relapse after 6 mths after allogeneic HSCT low IT	3	1	4
Baseline Eastern Cooperative Oncology Group (ECOG)			
ECOG performance status is a scale used to assess impact on daily activities. It is based on the investigator assessment. Scores range from 0 to 5, with 0-signifying fully active participant; 1-restricted in physically strenuous activity; 2-ambulatory and capable of all self-care, unable to work; 3-capable of only limited self-care, confined to bed more than 50% of waking hours; 4-completely disabled and 5-dead. Negative numerical score indicates an improvement and positive numerical score indicates a decline in participant's daily activities, indicating disease progression.			
Units: Subjects			
0-1	206	105	311
>=2	41	19	60
FLT3 Mutation Status: Central Testing by FLT3 CDx			
Units: Subjects			
FLT3-ITD Alone	215	113	328
FLT3-TKD Alone	21	10	31
FLT3-ITD and FLT3-TKD	7	0	7
Others (Unknown/Missing/Negative)	4	1	5
Prior Use of FLT3 Inhibitor			
Prior use of FLT3 inhibitor is defined as 'Yes' if participants received prior AML therapy of midostaurin, sorafenib or quizartinib; otherwise, prior use of FLT3 inhibitor is assigned as No.			
Units: Subjects			

No	215	110	325
Yes	32	14	46
Region			
Units: Subjects			
NORTH AMERICA	114	52	166
EUROPE	68	43	111
ASIA	65	29	94
Response to First Line Therapy			
Baseline stratification factors.			
Units: Subjects			
Primary refractory without HSCT	98	48	146
Relapse within 6 months after CRc and no HSCT	67	34	101
Relapse after 6 months after CRc and no HSCT	34	17	51
Relapse within 6 months after allogeneic HSCT	31	17	48
Relapse after 6 months after allogeneic HSCT	17	8	25
Preselected Salvage Chemotherapy			
Baseline stratification factors.			
Units: Subjects			
High intensity chemotherapy	149	75	224
Low intensity chemotherapy	98	49	147
Baseline Body Surface Area (BSA)			
Measure Analysis Population Description: The analysis population was the ITT, with available data.			
Units: m <sup>2</sup>			
arithmetic mean	1.815	1.777	
standard deviation	± 0.281	± 0.257	-
Baseline Weight			
Measure Analysis Population Description: The analysis population was the ITT, with available data.			
Units: kg			
arithmetic mean	72.79	69.91	
standard deviation	± 20.47	± 19.73	-
Baseline Height			
Measure Analysis Population Description: The analysis population was the ITT, with available data.			
Units: cm			
arithmetic mean	167.25	166.39	
standard deviation	± 10.31	± 10.63	-

## End points

### End points reporting groups

Reporting group title	Gilteritinib
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#### Reporting group description:

Participants received 120 mg dose (3 tablets of 40 mg) orally once a day in continuous 28-day cycles, at least 2 hours after or 1 hour before food. Gilteritinib treatment continued until participants met one of the treatment discontinuation criteria. After the end of treatment period, participants were allowed to enter long-term follow up period for up to 3 years for collection of subsequent AML treatment, EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L), remission status and survival (cause of death and date of death). Participants continuing to derive clinical benefit from gilteritinib as assessed by the investigator were allowed to continue the study treatment until a discontinuation criterion was met or if they had completed more than 3 years of treatment.

Reporting group title	Salvage Chemotherapy
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#### Reporting group description:

Participants received chemotherapy in 28-day cycles. Low-Dose Cytarabine (LoDAC): 20 mg of cytarabine twice daily by subcutaneous (SC)/intravenous (IV) injection for 10 days. Participants on azacitidine: 75 mg/m<sup>2</sup> daily by SC/IV injection for 7 days. Participants on LoDAC or azacitidine treatment continued until they met discontinuation criteria. MEC chemotherapy: mitoxantrone 8 mg/m<sup>2</sup> daily by IV for 5 days, etoposide 100 mg/m<sup>2</sup> daily by IV for 5 days and cytarabine 1000 mg/m<sup>2</sup> daily by IV for 5 days (days 1-5). FLAG-IDA chemotherapy: G-CSF 300 µg/m<sup>2</sup> daily by SC/IV for 5 days (days 1-5), fludarabine 30 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6), cytarabine 2000 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6) and idarubicin 10 mg/m<sup>2</sup> daily by IV for 3 days (days 2-4). MEC or FLAG-IDA: 1 cycle of therapy and were assessed on/after day 15. Participants were allowed to enter LTFU period of up to 3 years for collection of subsequent AML treatment, EQ-5D-5L, remission status and survival.

Reporting group title	Gilteritinib
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#### Reporting group description:

Participants received 120 mg dose (3 tablets of 40 mg) orally once a day in continuous 28-day cycles, at least 2 hours after or 1 hour before food. Gilteritinib treatment continued until participants met one of the treatment discontinuation criteria.

Reporting group title	Salvage Chemotherapy
-----------------------	----------------------

#### Reporting group description:

Participants received chemotherapy in 28-day cycles. Participants on Low-Dose Cytarabine (LoDAC) received 20 mg of cytarabine twice daily by subcutaneous (SC) or intravenous (IV) injection for 10 days. Participants on azacitidine received 75 mg/m<sup>2</sup> daily by SC or IV injection for 7 days. Participants on LoDAC or azacitidine treatment continued until they met discontinuation criteria. Participants on MEC chemotherapy received mitoxantrone 8 mg/m<sup>2</sup> daily by IV for 5 days, etoposide 100 mg/m<sup>2</sup> daily by IV for 5 days and cytarabine 1000 mg/m<sup>2</sup> daily by IV for 5 days (days 1-5). Participants on FLAG-IDA chemotherapy received G-CSF 300 µg/m<sup>2</sup> daily by SC/IV for 5 days (days 1-5), fludarabine 30 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6), cytarabine 2000 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6) and idarubicin 10 mg/m<sup>2</sup> daily by IV for 3 days (days 2-4). Participants receiving MEC or FLAG-IDA received 1 cycle of therapy and were assessed for response on or after day 15.

### Primary: Duration of Overall Survival (OS)

End point title	Duration of Overall Survival (OS)
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#### End point description:

Overall survival was defined as the time from the date of randomization until the date of death from any cause (death date – randomization 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 – randomized date + 1). The date of last contact was the latest date that the participant was known to be alive. The last contact date was derived for participants alive at the analysis cutoff date. Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula. The analysis population was the Intention to Treatment (ITT) which consisted of all randomized participants.

End point type	Primary
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#### End point timeframe:

From randomization to until the date of death from any cause (median time of follow-up for OS was 17.8 months)

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	124		
Units: months				
median (confidence interval 95%)	9.3 (7.7 to 10.7)	5.6 (4.7 to 7.3)		

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Stratified analysis where stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.0004 <sup>[2]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.637
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.83

Notes:

[1] - Based on Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm.

[2] - 1-sided P-value

## Primary: Percentage of Participants With Complete Remission and Complete Remission with Partial Hematological Recovery (CR/CRh) in the Gilteritinib Arm

End point title	Percentage of Participants With Complete Remission and Complete Remission with Partial Hematological Recovery (CR/CRh) in the Gilteritinib Arm <sup>[3][4]</sup>
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End point description:

CR/CRh rate: achieved either CR or CRh divided by number of participants in analysis population. CR: bone marrow regenerating normal hematopoietic cells and achieved a morphologic leukemia-free state and must had an ANC  $\geq 1 \times 10^9/L$  and platelet count  $\geq 100 \times 10^9/L$  and normal marrow differential with < 5% blasts, and they were RBC and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). No evidence of extramedullary leukemia. CRh: CRh: if they had marrow blasts < 5%, partial hematologic recovery ANC  $\geq 0.5 \times 10^9/L$  and platelets  $\geq 50 \times 10^9/L$ , no evidence of extramedullary leukemia and could not be classified as CR. Analysis population was the response analysis set (RAS) with participants who were 112 days past the first dose of gilteritinib/randomization. Participants were analyzed based on randomized treatments.

End point type	Primary
End point timeframe:	
From the date of randomization up to at least 112 days	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Per protocol no statistical analysis was performed for this endpoint.

[4] - 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: The coprimary endpoint of CR/CRh rate was analyzed for only the gilteritinib arm. The population analyzed was the response analysis set (RAS) with participants who were 112 days past the first dose of gilteritinib/randomization.

End point values	Gilteritinib			
Subject group type	Reporting group			
Number of subjects analysed	142			
Units: Percentage of participants				
number (confidence interval 95%)				
CR/CRh rate	28.2 (20.9 to 36.3)			
CR rate	19.0 (12.9 to 26.4)			
CRh rate	9.2 (5.0 to 15.1)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of Event-Free Survival (EFS)

End point title	Duration of Event-Free Survival (EFS)
End point description: EFS: time from randomization date up to date of documented relapse (excluding relapse after PR)/treatment failure (failure to achieve CR, CRp, CRi /PR) /death, whichever occurred first. Relapse: leukemic blasts in peripheral blood 5/ $\geq$ 25% blasts in bone marrow (BM) aspirate due to no other cause/reappearance/new appearance of extramedullary leukemia. CR: BM regenerating normal hematopoietic cells, morphologic leukemia-free state, ANC $\geq 1 \times 10^9/L$ , platelet count $\geq 100 \times 10^9/L$ , normal marrow differential with $< 5\%$ blasts, and RBC/platelet transfusion independent with no extramedullary leukemia. CRp: achieved CR except incomplete platelet recovery ( $< 100 \times 10^9/L$ ). CRi: criteria for CR fulfilled except incomplete hematological recovery with residual neutropenia $< 1 \times 10^9/L$ with /without complete platelet recovery. PR: BM regenerating normal hematopoietic cells, peripheral recovery, no circulating blasts & decrease of 50% blasts in with total blasts between 5% - 25% or, 5% if Auer rods present. ITT.	
End point type	Secondary
End point timeframe: From the date of randomization until the date of documented relapse, treatment failure or death from any cause (median time of follow-up was 17.8 months)	

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	62 <sup>[5]</sup>		
Units: months				
median (confidence interval 95%)	2.8 (1.4 to 3.7)	0.7 (0.2 to 99999)		

Notes:

[5] - 99999=Not Applicable. Data could not be estimated due to low number of events.

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description:	
Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
P-value	= 0.0415 <sup>[7]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.793
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.577
upper limit	1.089

Notes:

[6] - Based on the Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm.

[7] - 1-sided P-value

## Secondary: Percentage of Participants With Complete Remission (CR) Rate

End point title	Percentage of Participants With Complete Remission (CR) Rate
End point description:	
The CR rate was defined as the number of participants who achieved the best response of CR divided by the number of participants in the analysis population. CR: For participants to be classified as being in CR, they must have had bone marrow regenerating normal hematopoietic cells and achieved a morphologic leukemia-free state and must have had an ANC $\geq 1 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$ and normal marrow differential with $< 5\%$ blasts, and they were RBC and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). There was no evidence of extramedullary leukemia. The analysis population was the ITT.	
End point type	Secondary
End point timeframe:	
From the date of randomization up to at least 6 months	

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	124		
Units: Percentage of participants				
number (confidence interval 95%)	21.1 (16.1 to 26.7)	10.5 (5.7 to 17.3)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description:	
Based on stratified Cochran-Mantel-Haenszel test. Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT. Treatment difference = gilteritinib -chemotherapy.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0106 <sup>[8]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	10.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	18.4

Notes:

[8] - Stratified P-value

## Secondary: Duration of Leukemia-Free Survival (LFS)

End point title	Duration of Leukemia-Free Survival (LFS)
End point description:	
LFS: time from the date of first CRc until the date of documented relapse or death for subjects who achieve CRc. For a subject who is not known to have relapsed or died, LFS is censored on the date of last relapse-free disease assessment date. CRc: achieved CR, CRp or CRi. Relapse: leukemic blasts in peripheral blood/ $\geq 25\%$ blasts in bone marrow (BM) aspirate not due to any other cause/reappearance/new appearance of extramedullary leukemia. CR: BM regenerating normal hematopoietic cells, morphologic leukemia-free state, ANC $1 \times 10^9/L$ , platelet count $\geq 10 \times 10^9/L$ , normal marrow differential with $< 5\%$ blasts, and RBC/platelet transfusion independent with no extramedullary leukemia. CRp: achieved CR except incomplete platelet recovery ( $< 100 \times 10^9/L$ ). CRi : criteria for CR fulfilled except incomplete hematological recovery with residual neutropenia $< 1 \times 10^9/L$ with /without complete platelet recovery. The analysis population was the ITT, with participants with best response of CRc.	
End point type	Secondary
End point timeframe:	
From the date of first CRc until the date of documented relapse or death for participants who achieved CRc (median time of follow-up was 17.8 months)	

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	27		
Units: months				
median (confidence interval 95%)	4.4 (3.6 to 5.2)	6.7 (2.1 to 8.5)		

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
The LFS was analyzed for participants who achieved remission using the stratified log-rank test with strata to control for response to first-line AML therapy and preselected salvage chemotherapy. Duration of LFS was based on Kaplan-Meier estimates.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority <sup>[9]</sup>
P-value	= 0.6654 <sup>[10]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.506
upper limit	1.563

Notes:

[9] - Based on the Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm.

[10] - Unstratified p-value

## Secondary: Duration of Remission

End point title	Duration of Remission
End point description:	
Duration of remission included duration of CRc, CR/CRh, CRh, CR, CRi, CRp (defined as time from date of first CRc until date of first documented relapse for participants who achieved CRc, CR/CRh, CRh, CR, CRi, CRp respectively) & duration of response (CRc + PR). CRc:achieved CR, CRp or CRi at the visit. CR:BM regenerating normal hematopoietic cells, morphologic leukemia-free state, ANC $\geq 1 \times 10^9/L$ , platelet count $\geq 100 \times 10^9/L$ , normal marrow differential with <5% blasts, and RBC/platelet transfusion independent with no extramedullary leukemia. CRp:achieved CR except incomplete platelet recovery ( $< 100 \times 10^9/L$ ). CRi:criteria for CR fulfilled except incomplete hematological recovery with residual neutropenia $< 1 \times 10^9/L$ with /without complete platelet recovery. PR:BM regenerating normal hematopoietic cells, peripheral recovery, no circulating blasts and decrease of 50% blasts in with total blasts between 5% -25% or, 5% if Auer rods present. participants with best overall CR response analysed.	
End point type	Secondary
End point timeframe:	
From the date of either first CRc or PR until the date of documented relapse for participants who achieved CRc or PR (median time of follow-up was 17.8 months)	



End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52 <sup>[11]</sup>	13 <sup>[12]</sup>		
Units: months				
median (confidence interval 95%)	14.8 (11.0 to 99999)	1.8 (00000 to 99999)		

Notes:

[11] - 99999=Not Applicable. Data could not be estimated due to low number of events.

[12] - 00000 and 99999=Not Applicable. Data could not be estimated due to low number of events.

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority <sup>[13]</sup>
P-value	= 0.1189 <sup>[14]</sup>
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	1.886

Notes:

[13] - Based on Cox proportional hazards model. Assuming proportional hazards, a hazard ratio < 1 indicates a reduction in hazard rate in favor of gilteritinib arm.

[14] - Stratified p-value

## Secondary: Percentage of Participants With Composite Complete Remission (CRc Rate)

End point title	Percentage of Participants With Composite Complete Remission (CRc Rate)
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End point description:

CRc rate: Number of participants with best response of CRc (CR,complete remission with incomplete platelet recovery [CRp] or complete remission with incomplete hematologic recovery [CRi]) divided by number of participants in the analysis population. CRc : Participants who achieved CR, CRp or CRi at a post-baseline visit. CR: Participants having bone marrow regenerating normal hematopoietic cells, a morphologic leukemia-free state, an ANC  $\geq 1 \times 10^9/L$  and platelet count  $\geq 100 \times 10^9/L$ , normal marrow differential with < 5% blasts, and being RBC and platelet transfusion independent with no evidence of extramedullary leukemia at a post-baseline visit. CRp: Participants achieving CR except for incomplete platelet recovery ( $< 100 \times 10^9/L$ ) at a post-baseline visit. CRi : Participants, who fulfilled all criteria for CR except incomplete hematological recovery with residual neutropenia  $< 1 \times 10^9/L$  with or without complete platelet recovery at a post-baseline visit. ITT population analysed.

End point type	Secondary
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End point timeframe:

From the date of randomization up to at least 6 months

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	124		
Units: Percentage of participants				
number (confidence interval 95%)	54.3 (47.8 to 60.6)	21.8 (14.9 to 30.1)		

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Treatment difference = gilteritinib – chemotherapy. The 95% CIs were asymptotic confidence limits using the normal approximation to the binomial distribution.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[15]</sup>
Method	Fisher exact
Parameter estimate	Treatment difference
Point estimate	32.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.3
upper limit	42.6

Notes:

[15] - Unstratified 2-sided P-value

## Secondary: Percentage of Participants Who Underwent Hematopoietic Stem Cell Transplant

End point title	Percentage of Participants Who Underwent Hematopoietic Stem Cell Transplant
End point description:	
Transplantation rate was defined as the percentage of participants who underwent Hematopoietic stem cell transplant (HSCT) during the study period. The analysis population is the ITT.	
End point type	Secondary
End point timeframe:	
From the date of randomization until end of study (median time of follow-up was 17.8 months)	

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	124		
Units: Percentage of participants				
number (confidence interval 95%)	25.5 (20.2 to 31.4)	15.3 (9.5 to 22.9)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority <sup>[16]</sup>
P-value	= 0.0333 <sup>[17]</sup>
Method	Fisher exact
Parameter estimate	Treatment Difference
Point estimate	10.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	19.1

Notes:

[16] - Treatment difference = gilteritinib – chemotherapy

[17] - Unstratified 2-sided P-value.

## Secondary: Change From Baseline in Brief Fatigue Inventory (BFI)

End point title	Change From Baseline in Brief Fatigue Inventory (BFI)
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End point description:

BFI was a screening tool designed to assess the severity and impact of fatigue on daily functioning of participants with cancer during 24 hours. There are 9 items on the scale. The first three questions asked participants to rate their fatigues on a scale from 0 (no fatigue) - 10 (as bad as you can imagine), with higher scores indicating worse outcome. Next six questions asked participants to rate fatigue interference with their daily activities on a scale from 0 (Does not interfere) to 10 (Completely interferes). Global fatigue score can be obtained by averaging all items on the BFI. Total score range is 0-10 with a higher BFI fatigue score indicating worse outcome. Global BFI score was calculated only if at least 5 of the 9 items were answered. Analysis population: ITT, with participants with data at baseline. SAP pre-specified that 95% Confidence Interval would not be analyzed for this endpoint, 2-Sides (-99999, 99999) was entered to remove validation error.

End point type	Secondary
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End point timeframe:

Baseline and cycle 1 day 8 and cycle 2 day 1

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	97		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Cycle 1 day 8(C1D8) (n=191,73)	-0.4 (± 2.1)	1.0 (± 2.3)		
Cycle 2 day 1(C2D1) (n=206,15)	0.0 (± 2.6)	0.4 (± 2.8)		

## Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description:	
C2D1: Using analysis of covariance (ANCOVA) including treatment as a fixed factor, baseline score, response to first-line AML therapy and preselected salvage chemotherapy per IRT as covariates. Least Square (LS) Mean difference was estimated using chemotherapy as control.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.1574
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99999
upper limit	99999

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description:	
C1D8: Using analysis of covariance (ANCOVA) including treatment as a fixed factor, baseline score, response to first-line AML therapy and preselected salvage chemotherapy per IRT as covariates. Least Square (LS) Mean difference was estimated using chemotherapy as control.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0
Method	ANCOVA
Parameter estimate	Least square mean difference
Point estimate	-1.2567
Confidence interval	
level	95 %
sides	2-sided
lower limit	-99999
upper limit	99999

## Secondary: Percentage of Participants With Complete Remission (CR) With Partial Hematological Recovery (CRh)

End point title	Percentage of Participants With Complete Remission (CR) With Partial Hematological Recovery (CRh)
End point description:	
CRh rate was defined as the number of participants who achieved CRh at any of the postbaseline visits and did not have a best response of CR divided by the number of participants in the analysis population. CR: For participants to be classified as being in CR at a post-baseline visit, they must have had bone marrow regenerating normal hematopoietic cells and achieved a morphologic leukemia-free state and must had an ANC $\geq 1 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$ and normal marrow differential with $< 5\%$ blasts, and they were RBC and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). There was no evidence of extramedullary leukemia. CRh:At a post baseline visit, participantss were classified as CRh if they had marrow blasts $< 5\%$ , partial hematologic recovery ANC $\geq 0.5 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$ , no evidence of extramedullary leukemia and could not be classified as CR. The analysis population was the ITT.	
End point type	Secondary
End point timeframe:	
From the date of randomization up to at least 6 months	

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	124		
Units: Percentage of participants				
number (confidence interval 95%)	34.0 (28.1 to 40.3)	15.3 (9.5 to 22.9)		

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Based on a stratified Cochran-Mantel-Haenszel test. Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT. Pooled strata were used as shown in Table 12.3.3.2.Treatment differences were adjusted based on pooled strata. Treatment difference = gilteritinib 120 mg –chemotherapy.	
Comparison groups	Gilteritinib v Salvage Chemotherapy
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	
P-value	$< 0.0171$ <sup>[18]</sup>
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted Treatment Difference
Point estimate	18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.8
upper limit	27.4

Notes:

[18] - Stratified 1-sided P-value

## Secondary: Percentage of Participants Who Achieved Transfusion Conversion and

## Maintenance

End point title	Percentage of Participants Who Achieved Transfusion Conversion and Maintenance <sup>[19]</sup>
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End point description:

Transfusion conversion & maintenance rate was defined for gilteritinib arm. Participants were classified as transfusion independent if there were no RBC or platelet transfusions within 28 days prior to the first dose to 28 days after the first dose; otherwise they were classified as transfusion dependent at baseline. Participants were considered independent postbaseline if they had 1 consecutive 8 week period without any RBC or platelet transfusion from 29 days after the first dose until the last dose date. For participants who were on treatment  $\leq 4$  weeks or  $> 4$  weeks but  $< 12$  weeks and there was no RBC or platelet transfusion within postbaseline period, they were considered not evaluable; otherwise, they were considered postbaseline transfusion dependent. Transfusion conversion rate was defined for participants who had evaluable postbaseline transfusion status. Transfusion status (independent vs. dependent) at baseline and postbaseline was reported in a 2 by 2 contingency table.

End point type	Secondary
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End point timeframe:

From 29 days post first dose of study drug until last dose (median treatment duration was (126.00 [4.0, 885.0])

Notes:

[19] - 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: Transfusion conversion rate and transfusion maintenance rate were only defined for the patients in the gilteritinib arm.

End point values	Gilteritinib			
Subject group type	Reporting group			
Number of subjects analysed	246			
Units: Percentage of participants				
number (not applicable)				
Baseline Independent/ Postbaseline Independent	59.2			
Baseline Independent/Postbaseline Dependent	24.5			
Baseline Independent/Postbaseline Not Evaluable	16.3			
Baseline Dependent/Postbaseline Independent	34.5			
Baseline Dependent/Postbaseline Dependent	55.8			
Baseline Dependent/Postbaseline Not Evaluable	9.6			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Treatment Emergent Adverse Events

End point title	Number of Participants with Treatment Emergent Adverse Events
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End point description:

An AE was defined as any untoward medical occurrence in a participant, temporally associated with study drug use, whether/not related to it, such as any unfavorable/unintended sign (including abnormal laboratory finding), symptom/disease (new/exacerbated). Treatment-emergent adverse event (TEAE) : AEs observed after starting administration of study drug Serious AEs (SAEs): AEs which caused death, were life-threatening, resulted in persistent/significant disability/incapacity or disruption of the ability to

conduct normal life functions, congenital anomaly, birth defect, required inpatient hospitalization/led to prolongation of hospitalization. Based on national cancer institute common terminology criteria (NCI-CTCAE), AEs were graded as grade 1=mild, grade 2=moderate, grade 3 =severe or medically significant, grade 4 =life threatening, grade 5 =death related to AE. Safety analysis set (SAF), with participants who received who received at least 1 dose of study drug was analysed.

End point type	Secondary
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End point timeframe:

From first dose of study drug up to 30 days after the last dose of study drug (median treatment duration for gilteritinib was (126.00 [4.0, 885.0]) days versus salvage chemotherapy 28.0 [5.0, 217.0] days)

End point values	Gilteritinib	Salvage Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	109		
Units: Participants				
Drug-related TEAE	208	71		
Serious TEAE	211	34		
Drug-related serious TEAE	92	16		
TEAE leading to death	76	16		
Drug-related TEAE leading to death	11	5		
TEAE leading to withdrawal of treatment	65	13		
Drug-related TEAE lead withdrawal of treatment	30	5		
NCI-CTCAE Grade 3 or higher TEAE	238	94		
Drug-related Grade 3 or higher TEAE	157	57		
Death	203	87		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 30 days after the last dose of study drug (median treatment duration for gilteritinib was (126.00 [4.0, 885.0]) days versus salvage chemotherapy 28.0 [5.0, 217.0] days).

Adverse event reporting additional description:

The SAF consisted of all participants who received at least dose of study treatment (gilteritinib or salvage chemotherapy).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	v23
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### Reporting groups

Reporting group title	Gilteritinib
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Reporting group description:

Participants received 120 mg dose (3 tablets of 40 mg) orally once a day in continuous 28-day cycles, at least 2 hours after or 1 hour before food. Gilteritinib treatment continued until participants met one of the treatment discontinuation criteria. After the end of treatment period, participants were allowed to enter long-term follow up period for up to 3 years for collection of subsequent AML treatment, EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L), remission status and survival (cause of death and date of death). Participants continuing to derive clinical benefit from gilteritinib as assessed by the investigator were allowed to continue the study treatment until a discontinuation criterion was met or if they had completed more than 3 years of treatment.

Reporting group title	Salvage Chemotherapy
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Reporting group description:

Participants received chemotherapy in 28-day cycles. Low-Dose Cytarabine (LoDAC): 20 mg of cytarabine twice daily by subcutaneous (SC)/intravenous (IV) injection for 10 days. Participants on azacitidine: 75 mg/m<sup>2</sup> daily by SC/IV injection for 7 days. Participants on LoDAC or azacitidine treatment continued until they met discontinuation criteria. MEC chemotherapy: mitoxantrone 8 mg/m<sup>2</sup> daily by IV for 5 days, etoposide 100 mg/m<sup>2</sup> daily by IV for 5 days and cytarabine 1000 mg/m<sup>2</sup> daily by IV for 5 days (days 1-5). FLAG-IDA chemotherapy: G-CSF 300 µg/m<sup>2</sup> daily by SC/IV for 5 days (days 1-5), fludarabine 30 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6), cytarabine 2000 mg/m<sup>2</sup> daily by IV for 5 days (days 2-6) and idarubicin 10 mg/m<sup>2</sup> daily by IV for 3 days (days 2-4). MEC or FLAG-IDA: 1 cycle of therapy and were assessed on/after day 15. Participants were allowed to enter LTFU period of up to 3 years for collection of subsequent AML treatment, EQ-5D-5L, remission status and survival.

Serious adverse events	Gilteritinib	Salvage Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	211 / 246 (85.77%)	34 / 109 (31.19%)	
number of deaths (all causes)	204	96	
number of deaths resulting from adverse events	76	16	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	



Acute myeloid leukaemia			
subjects affected / exposed	35 / 246 (14.23%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	0 / 40	0 / 6	
deaths causally related to treatment / all	0 / 29	0 / 4	
Acute myeloid leukaemia recurrent			
subjects affected / exposed	7 / 246 (2.85%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 9	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system leukaemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia cutis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia recurrent			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant neoplasm progression			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm malignant			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue sarcoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 246 (2.44%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	3 / 246 (1.22%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Face oedema			

subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 246 (1.63%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	34 / 246 (13.82%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	2 / 45	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 246 (0.81%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease in intestine			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	10 / 246 (4.07%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 11	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypoxia			
subjects affected / exposed	4 / 246 (1.63%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obliterative bronchiolitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Productive cough			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	3 / 246 (1.22%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	8 / 246 (3.25%)	3 / 109 (2.75%)	
occurrences causally related to treatment / all	3 / 9	4 / 5	
deaths causally related to treatment / all	1 / 2	2 / 2	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			



subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	13 / 246 (5.28%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	15 / 17	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 246 (4.07%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	14 / 14	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			

subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood fibrinogen decreased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ejection fraction decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menstruation normal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	6 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus test positive			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	5 / 246 (2.03%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	6 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic transfusion reaction			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	8 / 246 (3.25%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Accessory breast			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hamartoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Myocarditis			

subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amnesia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			



subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Headache			
subjects affected / exposed	5 / 246 (2.03%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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	7 / 246 (2.85%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Aplasia pure red cell			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	76 / 246 (30.89%)	9 / 109 (8.26%)	
occurrences causally related to treatment / all	28 / 113	3 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	8 / 246 (3.25%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	6 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 246 (1.63%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 246 (1.22%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukocytosis			
subjects affected / exposed	2 / 246 (0.81%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness bilateral			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastritis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	11 / 246 (4.47%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	3 / 14	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Melaena			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Nausea			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis necrotising			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue haematoma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petechiae			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	18 / 246 (7.32%)	4 / 109 (3.67%)	
occurrences causally related to treatment / all	3 / 23	2 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematuria			



subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			

subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	10 / 246 (4.07%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 11	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess bacterial			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenoviral upper respiratory infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	6 / 246 (2.44%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	5 / 246 (2.03%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial infection			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial colitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr viraemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	4 / 246 (1.63%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leptotrichia infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 246 (1.22%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infection			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatic infection			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection toxoplasma			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection bacterial			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	3 / 246 (1.22%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital infection			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	43 / 246 (17.48%)	8 / 109 (7.34%)	
occurrences causally related to treatment / all	15 / 66	6 / 12	
deaths causally related to treatment / all	3 / 7	1 / 2	
Respiratory tract infection fungal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			



subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia fungal			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	19 / 246 (7.72%)	7 / 109 (6.42%)	
occurrences causally related to treatment / all	3 / 24	5 / 11	
deaths causally related to treatment / all	1 / 5	2 / 3	
Septic shock			
subjects affected / exposed	10 / 246 (4.07%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	3 / 17	0 / 1	
deaths causally related to treatment / all	2 / 8	0 / 1	
Sinusitis			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			

subjects affected / exposed	4 / 246 (1.63%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	6 / 246 (2.44%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	3 / 246 (1.22%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic bacterial infection			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mycosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tooth abscess			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 246 (2.03%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	2 / 246 (0.81%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (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	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cellulitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Adult failure to thrive			

subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 246 (0.41%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperphosphataemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 246 (0.81%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemic syndrome			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 246 (0.41%)	2 / 109 (1.83%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Gilteritinib	Salvage Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	242 / 246 (98.37%)	103 / 109 (94.50%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	35 / 246 (14.23%)	10 / 109 (9.17%)	
occurrences (all)	77	10	
Hypotension			
subjects affected / exposed	40 / 246 (16.26%)	7 / 109 (6.42%)	
occurrences (all)	47	8	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	93 / 246 (37.80%)	31 / 109 (28.44%)	
occurrences (all)	147	57	
Pain			
subjects affected / exposed	17 / 246 (6.91%)	1 / 109 (0.92%)	
occurrences (all)	21	1	
Oedema peripheral			
subjects affected / exposed	61 / 246 (24.80%)	13 / 109 (11.93%)	
occurrences (all)	80	19	
Oedema			
subjects affected / exposed	15 / 246 (6.10%)	3 / 109 (2.75%)	
occurrences (all)	18	3	
Mucosal inflammation			
subjects affected / exposed	13 / 246 (5.28%)	9 / 109 (8.26%)	
occurrences (all)	13	11	
Fatigue			
subjects affected / exposed	71 / 246 (28.86%)	14 / 109 (12.84%)	
occurrences (all)	102	17	
Chills			
subjects affected / exposed	23 / 246 (9.35%)	8 / 109 (7.34%)	
occurrences (all)	33	9	
Asthenia			
subjects affected / exposed	35 / 246 (14.23%)	10 / 109 (9.17%)	
occurrences (all)	49	11	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	16 / 246 (6.50%)	1 / 109 (0.92%)	
occurrences (all)	22	1	
Respiratory, thoracic and mediastinal disorders			
Productive cough			
subjects affected / exposed	18 / 246 (7.32%)	2 / 109 (1.83%)	
occurrences (all)	23	2	
Pleural effusion			
subjects affected / exposed	17 / 246 (6.91%)	2 / 109 (1.83%)	
occurrences (all)	18	3	
Oropharyngeal pain			

subjects affected / exposed	21 / 246 (8.54%)	8 / 109 (7.34%)	
occurrences (all)	24	8	
Nasal congestion			
subjects affected / exposed	18 / 246 (7.32%)	1 / 109 (0.92%)	
occurrences (all)	21	1	
Cough			
subjects affected / exposed	72 / 246 (29.27%)	11 / 109 (10.09%)	
occurrences (all)	102	13	
Dyspnoea			
subjects affected / exposed	52 / 246 (21.14%)	7 / 109 (6.42%)	
occurrences (all)	70	8	
Dyspnoea exertional			
subjects affected / exposed	16 / 246 (6.50%)	0 / 109 (0.00%)	
occurrences (all)	19	0	
Epistaxis			
subjects affected / exposed	42 / 246 (17.07%)	8 / 109 (7.34%)	
occurrences (all)	51	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	19 / 246 (7.72%)	1 / 109 (0.92%)	
occurrences (all)	22	1	
Depression			
subjects affected / exposed	13 / 246 (5.28%)	7 / 109 (6.42%)	
occurrences (all)	16	7	
Insomnia			
subjects affected / exposed	42 / 246 (17.07%)	6 / 109 (5.50%)	
occurrences (all)	46	6	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	100 / 246 (40.65%)	10 / 109 (9.17%)	
occurrences (all)	249	20	
Aspartate aminotransferase increased			
subjects affected / exposed	97 / 246 (39.43%)	13 / 109 (11.93%)	
occurrences (all)	253	21	
Blood alkaline phosphatase increased			

subjects affected / exposed	55 / 246 (22.36%)	2 / 109 (1.83%)
occurrences (all)	113	2
Blood bilirubin increased		
subjects affected / exposed	21 / 246 (8.54%)	7 / 109 (6.42%)
occurrences (all)	68	9
Blood creatine phosphokinase increased		
subjects affected / exposed	35 / 246 (14.23%)	0 / 109 (0.00%)
occurrences (all)	111	0
Blood creatinine increased		
subjects affected / exposed	32 / 246 (13.01%)	4 / 109 (3.67%)
occurrences (all)	78	4
Blood lactate dehydrogenase increased		
subjects affected / exposed	24 / 246 (9.76%)	5 / 109 (4.59%)
occurrences (all)	35	5
Electrocardiogram QT prolonged		
subjects affected / exposed	16 / 246 (6.50%)	0 / 109 (0.00%)
occurrences (all)	19	0
International normalised ratio increased		
subjects affected / exposed	14 / 246 (5.69%)	5 / 109 (4.59%)
occurrences (all)	18	6
Neutrophil count decreased		
subjects affected / exposed	40 / 246 (16.26%)	12 / 109 (11.01%)
occurrences (all)	167	28
Platelet count decreased		
subjects affected / exposed	54 / 246 (21.95%)	28 / 109 (25.69%)
occurrences (all)	253	76
Weight decreased		
subjects affected / exposed	13 / 246 (5.28%)	3 / 109 (2.75%)
occurrences (all)	21	4
White blood cell count decreased		
subjects affected / exposed	34 / 246 (13.82%)	19 / 109 (17.43%)
occurrences (all)	130	27
Weight increased		



subjects affected / exposed occurrences (all)	14 / 246 (5.69%) 18	2 / 109 (1.83%) 6	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	10 / 246 (4.07%)	7 / 109 (6.42%)	
occurrences (all)	17	13	
Contusion			
subjects affected / exposed	14 / 246 (5.69%)	3 / 109 (2.75%)	
occurrences (all)	18	3	
Fall			
subjects affected / exposed	19 / 246 (7.72%)	1 / 109 (0.92%)	
occurrences (all)	28	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	13 / 246 (5.28%)	7 / 109 (6.42%)	
occurrences (all)	14	7	
Atrial fibrillation			
subjects affected / exposed	13 / 246 (5.28%)	1 / 109 (0.92%)	
occurrences (all)	15	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	48 / 246 (19.51%)	2 / 109 (1.83%)	
occurrences (all)	66	2	
Dysgeusia			
subjects affected / exposed	22 / 246 (8.94%)	4 / 109 (3.67%)	
occurrences (all)	26	4	
Headache			
subjects affected / exposed	62 / 246 (25.20%)	16 / 109 (14.68%)	
occurrences (all)	89	18	
Paraesthesia			
subjects affected / exposed	22 / 246 (8.94%)	0 / 109 (0.00%)	
occurrences (all)	27	0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	57 / 246 (23.17%)	32 / 109 (29.36%)	
occurrences (all)	73	37	

Disseminated intravascular coagulation subjects affected / exposed occurrences (all)	8 / 246 (3.25%) 9	6 / 109 (5.50%) 6	
Anaemia subjects affected / exposed occurrences (all)	112 / 246 (45.53%) 493	38 / 109 (34.86%) 80	
Neutropenia subjects affected / exposed occurrences (all)	32 / 246 (13.01%) 115	16 / 109 (14.68%) 18	
Thrombocytopenia subjects affected / exposed occurrences (all)	62 / 246 (25.20%) 301	17 / 109 (15.60%) 41	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	20 / 246 (8.13%) 22	1 / 109 (0.92%) 1	
Retinal haemorrhage subjects affected / exposed occurrences (all)	20 / 246 (8.13%) 23	2 / 109 (1.83%) 2	
Dry eye subjects affected / exposed occurrences (all)	27 / 246 (10.98%) 28	3 / 109 (2.75%) 3	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	82 / 246 (33.33%) 136	32 / 109 (29.36%) 37	
Constipation subjects affected / exposed occurrences (all)	77 / 246 (31.30%) 96	16 / 109 (14.68%) 18	
Abdominal pain upper subjects affected / exposed occurrences (all)	13 / 246 (5.28%) 18	3 / 109 (2.75%) 5	
Abdominal pain subjects affected / exposed occurrences (all)	37 / 246 (15.04%) 44	16 / 109 (14.68%) 17	
Vomiting			

subjects affected / exposed	57 / 246 (23.17%)	15 / 109 (13.76%)	
occurrences (all)	89	16	
Stomatitis			
subjects affected / exposed	35 / 246 (14.23%)	15 / 109 (13.76%)	
occurrences (all)	46	19	
Nausea			
subjects affected / exposed	83 / 246 (33.74%)	36 / 109 (33.03%)	
occurrences (all)	129	41	
Mouth ulceration			
subjects affected / exposed	13 / 246 (5.28%)	2 / 109 (1.83%)	
occurrences (all)	14	2	
Dry mouth			
subjects affected / exposed	22 / 246 (8.94%)	3 / 109 (2.75%)	
occurrences (all)	23	3	
Dyspepsia			
subjects affected / exposed	13 / 246 (5.28%)	7 / 109 (6.42%)	
occurrences (all)	16	7	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	15 / 246 (6.10%)	3 / 109 (2.75%)	
occurrences (all)	19	3	
Rash maculo-papular			
subjects affected / exposed	11 / 246 (4.47%)	6 / 109 (5.50%)	
occurrences (all)	16	6	
Rash			
subjects affected / exposed	37 / 246 (15.04%)	10 / 109 (9.17%)	
occurrences (all)	55	10	
Pruritus			
subjects affected / exposed	25 / 246 (10.16%)	4 / 109 (3.67%)	
occurrences (all)	30	4	
Erythema			
subjects affected / exposed	14 / 246 (5.69%)	4 / 109 (3.67%)	
occurrences (all)	18	4	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed occurrences (all)	19 / 246 (7.72%) 21	5 / 109 (4.59%) 6	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	36 / 246 (14.63%)	4 / 109 (3.67%)	
occurrences (all)	48	4	
Arthralgia			
subjects affected / exposed	32 / 246 (13.01%)	6 / 109 (5.50%)	
occurrences (all)	49	8	
Back pain			
subjects affected / exposed	33 / 246 (13.41%)	13 / 109 (11.93%)	
occurrences (all)	37	13	
Bone pain			
subjects affected / exposed	14 / 246 (5.69%)	3 / 109 (2.75%)	
occurrences (all)	16	4	
Muscular weakness			
subjects affected / exposed	19 / 246 (7.72%)	1 / 109 (0.92%)	
occurrences (all)	22	2	
Musculoskeletal pain			
subjects affected / exposed	14 / 246 (5.69%)	2 / 109 (1.83%)	
occurrences (all)	16	3	
Pain in extremity			
subjects affected / exposed	37 / 246 (15.04%)	8 / 109 (7.34%)	
occurrences (all)	45	11	
Infections and infestations			
Cellulitis			
subjects affected / exposed	15 / 246 (6.10%)	1 / 109 (0.92%)	
occurrences (all)	17	2	
Nasopharyngitis			
subjects affected / exposed	13 / 246 (5.28%)	2 / 109 (1.83%)	
occurrences (all)	25	2	
Oral candidiasis			
subjects affected / exposed	13 / 246 (5.28%)	3 / 109 (2.75%)	
occurrences (all)	14	3	
Pneumonia			

subjects affected / exposed	40 / 246 (16.26%)	5 / 109 (4.59%)	
occurrences (all)	46	5	
Sinusitis			
subjects affected / exposed	15 / 246 (6.10%)	2 / 109 (1.83%)	
occurrences (all)	21	3	
Upper respiratory tract infection			
subjects affected / exposed	21 / 246 (8.54%)	3 / 109 (2.75%)	
occurrences (all)	48	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	46 / 246 (18.70%)	20 / 109 (18.35%)	
occurrences (all)	58	22	
Dehydration			
subjects affected / exposed	14 / 246 (5.69%)	1 / 109 (0.92%)	
occurrences (all)	17	1	
Hyperglycaemia			
subjects affected / exposed	38 / 246 (15.45%)	13 / 109 (11.93%)	
occurrences (all)	64	18	
Hyperkalaemia			
subjects affected / exposed	24 / 246 (9.76%)	1 / 109 (0.92%)	
occurrences (all)	51	1	
Hyperuricaemia			
subjects affected / exposed	24 / 246 (9.76%)	2 / 109 (1.83%)	
occurrences (all)	33	2	
Hypoalbuminaemia			
subjects affected / exposed	33 / 246 (13.41%)	7 / 109 (6.42%)	
occurrences (all)	70	11	
Hypocalcaemia			
subjects affected / exposed	49 / 246 (19.92%)	6 / 109 (5.50%)	
occurrences (all)	113	14	
Hypokalaemia			
subjects affected / exposed	72 / 246 (29.27%)	33 / 109 (30.28%)	
occurrences (all)	194	48	
Hypomagnesaemia			
subjects affected / exposed	41 / 246 (16.67%)	12 / 109 (11.01%)	
occurrences (all)	71	15	

Hyponatraemia			
subjects affected / exposed	32 / 246 (13.01%)	6 / 109 (5.50%)	
occurrences (all)	78	7	
Hypophosphataemia			
subjects affected / exposed	43 / 246 (17.48%)	5 / 109 (4.59%)	
occurrences (all)	77	5	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2015	<p>Changes included:</p> <ul style="list-style-type: none"><li>• The entry criteria were modified:<ul style="list-style-type: none"><li>o Inclusion Criterion No. 2 was modified to clarify the eligibility age.</li><li>o Inclusion Criterion No. 4 (second bullet) was modified to define "relapsed after first-line therapy" as untreated relapse patients who had achieved CR/CRi/CRp with first-line treatment and had hematologic relapse.</li><li>o Exclusion Criterion No. 4 was modified to exclude patients who experienced a hematologic relapse after their second or later line of treatment or who received salvage therapy for refractory disease.</li><li>o Exclusion Criterion No. 12 was modified to clarify that patients were excluded if they required treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.</li><li>o A separate exclusion criterion (Criterion No. 13) was added to exclude patients who required treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) or substrates of multidrug and toxin extrusion protein 1 (MATE1) with the exception of drugs that were considered absolutely essential for the care of the patient.</li><li>o An exclusion criterion (Criterion No. 19) was added to exclude patients with active graft-versus-host disease (GVHD) or who were on treatment with corticosteroids for GVHD.</li></ul></li><li>• Protocol language regarding concomitant medication restrictions or requirements was modified to clarify that patients who received treatment with strong inducers of CYP3A were excluded. In addition, the list of CYP3A inducers provided as an appendix to the protocol was revised to reflect strong CYP3A inducers as listed in the FDA Guidance for Drug Interaction Studies. The medications language was also modified to clarify the parameters for absolute blast count, remove the hydroxyurea daily dose limit, clarify that intrathecal chemotherapy should have been prophylactic, add cranial radiation as an allowed treatment of AML, and clarify that participation in another interventional study while on treatment was prohibited.</li></ul>

22 June 2015	<p>More changes included:</p> <ul style="list-style-type: none"> <li>• The treatment discontinuation criteria were amended: <ul style="list-style-type: none"> <li>o A discontinuation criterion was added to define lack of efficacy for a patient who was receiving LoDAC, azacitidine or gilteritinib.</li> <li>o A discontinuation criterion was modified to clarify that use of hydroxyurea was not a reason for discontinuation.</li> </ul> </li> <li>• Monitoring for the development of hyperuricemia was added.</li> <li>• PRO measurements of BFI, FACT-leu, FACIT-Dys-SF and dizziness/mouth sore were removed from the 30-day follow-up assessment.</li> <li>• Clinical efficacy and safety information were updated. • The baseline bone marrow aspiration, baseline blood platelet count and baseline white blood cell count were removed from the subgroup analysis.</li> </ul> <p>No patients were randomized under protocol Substantial Amendment 1; these changes to the protocol are not expected to substantively affect the overall interpretation of the study.</p> <ul style="list-style-type: none"> <li>• The guidelines for gilteritinib dose interruption or reduction were revised by deleting the requirement for 48 hours duration of Grade 3 AEs to interrupt dosing and state that treatment with gilteritinib was interrupted for any related Grade 3 AE.</li> <li>• The definition of transfusion independence was changed from 4 weeks to 1 week without red blood cell transfusion and 1 week without platelet transfusion.</li> </ul>
13 August 2015	<p>Changes Included:</p> <ul style="list-style-type: none"> <li>• The exclusion criteria were modified: <ul style="list-style-type: none"> <li>o Exclusion Criterion No.12 was added to exclude patients with mean Fridericia-corrected QT interval (QTcF) &gt; 450 msec at screening based on central reading.</li> <li>o Exclusion Criterion No.13 was added to exclude patients with Long QT Syndrome at screening.</li> <li>o Exclusion Criterion No.14 was added to exclude patients with hypokalemia and hypomagnesemia at screening (defined as values below the lower limit of normal [LLN]).</li> </ul> </li> <li>• HSCT was removed from the discontinuation criteria (fifth discontinuation criterion bullet).</li> <li>• 12-lead ECG and pharmacokinetic sampling was added (whole blood samples for plasma pharmacokinetic) to occur on day 8 ± 1 predose.</li> <li>• A confirmatory ECG that was to be performed on day 9 and an investigator assessment to consider a dose reduction for a patient if the mean QTcF for a patient from day 1 to day 8 had increased &gt; 30 msec with no other known etiology was added.</li> <li>• The mean QTcF of the triplicate ECG tracings based on central reading was clarified to be used for all treatment decisions.</li> <li>• The statement regarding relationship between QTcF interval prolongation and gilteritinib plasma concentrations was updated.</li> <li>• A criterion to the dose medication modification category was added to consider reducing the dose of gilteritinib if the mean QTcF from day 1 to day 8 had increased &gt; 30 msec, which was confirmed on day 9 without any other etiology.</li> </ul> <p>Thirty-six patients were randomized under protocol Substantial Amendment 2; these changes to the protocol are not expected to substantively affect the overall interpretation of the study.</p>



09 December 2015	<p>Changes included:</p> <ul style="list-style-type: none"> <li>• Clarification that if bone cellularity was between 5% and 20%, the investigator should have determined whether a patient should have received another treatment cycle was provided.</li> <li>• The description of acceptable contraception methods was changed for females in inclusion Criterion No. 10 and for males and their spouse/partners in inclusion Criterion No. 13.</li> <li>• The mean of triplicate QTcF &gt; 450 msec was clarified to be cause for exclusion in Criterion No. 12 and the terminology for Long QT Syndrome in exclusion Criterion No. 13 was modified. A precaution regarding the use of gilteritinib with concomitant medications that are known to prolong QT or corrected QT interval (QTc) was added and further instructions were provided to the investigator to check each patient's concomitant drugs for those that might have prolonged QT or QTc interval. In addition, a list of drugs that might have prolonged QT or QTc interval was added to the list of Excluded and Cautionary Concomitant Medications. A guideline for gilteritinib dose interruption and dose reduction if a patient had a mean of triplicate QTcF &gt; 500 msec was added.</li> <li>• The discontinuation criterion that patients receiving MEC or FLAG-IDA who had NR or progressive disease should have been discontinued if it occurred following cycle1 was clarified.</li> </ul>
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08 August 2016	<p>Changes included:</p> <ul style="list-style-type: none"> <li>• The long-term follow-up was clarified to be every 3 months for up to 3 years from the patient's end of treatment visit.</li> <li>• Midostaurin was included as a permitted prior treatment in exclusion Criterion No. 7.</li> <li>• Patients with disallowed FLT3 mutation types (exclusion Criterion No. 23) were excluded; patients were included on the basis of local laboratory testing for allowed FLT3 mutation types (inclusion Criterion No. 5).</li> <li>• Exclusion of MATE1 substrates as a concomitant medication restriction was deleted.</li> </ul> <p>Donor lymphocyte infusion as an allowed concomitant treatment for AML was included.</p> <ul style="list-style-type: none"> <li>• Discontinuation criteria were clarified to include language stating that patients were eligible to continue treatment until a discontinuation criterion was met or gilteritinib gained a marketing authorization and became commercially available.</li> <li>• Hazard ratio (HR) in the interim analysis was included.</li> <li>• Disease assessment from bone marrow samples was clarified to only be required for MEC and FLAG-IDA treatment per institutional guidelines on cycle 1 day 15 or later.</li> <li>• Gilteritinib clinical and pharmacokinetic data from the 02 Feb 2015 cut-off was updated with data from the 31 Oct 2015 cut-off.</li> <li>• Instructions to investigators regarding gilteritinib dose reduction and interruptions were clarified.</li> <li>• Methodology for assessment of exposure and compliance were clarified.</li> <li>• Laboratory tests administered were updated with the addition of thyroxine, thyroid-stimulating hormone and activated partial thromboplastin time. Language to clarify that 2 laboratories were assaying bone marrow samples for different parameters was added.</li> <li>• Purposes and conditions of the PGx substudy participation were updated to clarify that genes of relevance to AML patients may be analyzed in relationship to gilteritinib treatment, and that consenting patients may (instead of will) participate.</li> </ul>
20 September 2017	<p>Changes included:</p> <ul style="list-style-type: none"> <li>• A coprimary objective for Interim Analysis 1 and updated response definitions were added.</li> <li>• The secondary objectives and endpoints were updated.</li> <li>• Additional language was added to describe the collection of concomitant medications.</li> <li>• Additional language was added to describe the collection of AEs for patients who underwent HSCT.</li> <li>• Statistical analyses for key secondary efficacy endpoints, secondary endpoints and exploratory endpoints were updated.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported