Clinical trial results:
A Phase 2 Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission

Summary

EudraCT number	2016-001643-39
Trial protocol	HU ES CZ PL PT SE GR DK HR FR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	04 May 2022
First version publication date	04 May 2022

Trial information

Trial identification

Sponsor protocol code	2215-CL-0302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02927262
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical trial Disclosure, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical trial Disclosure, Astellas Pharma Global Development, Inc, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	25 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2021
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial: The primary objective of this study was to compare RFS between participants with FMS-like tyrosine kinase 3 (FLT3)/internal tandem duplication (ITD) acute myeloid leukemia (AML) in first complete remission (CR1) without transplant and who were randomized to receive gilteritinib or placebo beginning after completion of induction/consolidation chemotherapy for a 2-year period.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 18
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 1

Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	98
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	53
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult participants diagnosed with FLT3/ITD AML in first CR1, including complete remission with incomplete platelet recovery (CRp) and complete remission with incomplete hematologic recovery (CRi) for whom a decision not to proceed with transplantation was made, or a suitable donor could not be identified, were enrolled in this study

Pre-assignment

Screening details:

Randomization was stratified based on:
Age (<60 or ≥60 years), Geographic region (North America or Europe or Rest of the world), Presence of MRD at screening (yes or no), Use of FLT3-inhibiting agents during induction/consolidation (yes or no).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gilteritinib

Arm description:

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

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

Dosage and administration details:

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

Arm title	Placebo

Arm description:

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

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

Dosage and administration details:

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

Number of subjects in period 1	Gilteritinib	Placebo
Started	63	35
Completed	20	12
Not completed	43	23
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	-
Disease Relapse	23	18
Adverse event, non-fatal	7	1
Miscellaneous	5	4
Ongoing	4	-

Baseline characteristics

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

Reporting group values	Gilteritinib	Placebo	Total
Number of subjects	63	35	98
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	61.4	59.9	
standard deviation	± 11.0	± 13.9	-
Sex: Female, Male Units: Participants			
Female	31	20	51
Male	32	15	47
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	17	10	27
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	38	22	60
More than one race	0	0	0
Unknown or Not Reported	8	3	11
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	3	9
Not Hispanic or Latino	50	29	79
Unknown or Not Reported	7	3	10
Age (<60 or ≥60 years) Units: Subjects			
< 60 years	24	13	37
≥ 60 years	39	22	61
Geographic Region			
Geographical region was categorized as Europe, North America and Rest of the World.			
Units: Subjects			
North America	5	4	9
Europe	40	20	60

Rest of the world	18	11	29
Presence of MRD			
Presence of MRD (yes/no) at screening per interatcive response technology (IRT) at randomization was reported. The presence of MRD will be "Yes" if log10-transformed overall FLT3/ITD mutation ratio was greater than -4			
Units: Subjects			
MRD = Yes	8	6	14
MRD = No	55	29	84
Use of FLT3-inhibitors			
Use of FLT3 inhibitor (yes/no) during induction/consolidation per IRT at randomization was reported.			
Units: Subjects			
Use of FLT3 Inhibitor = Yes	12	10	22
Use of FLT3 Inhibitor = No	51	25	76

End points

End points reporting groups

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

Primary: Relapse-free Survival (RFS) per Independent Review Committee (IRC) Adjudication

End point title	Relapse-free Survival (RFS) per Independent Review Committee (IRC) Adjudication

End point description:

RFS was defined as time from the date of randomization until the date of documented relapse or death from any cause, whichever occurred first. Relapse after complete remission (CR) [including complete remission with incomplete platelet recovery (CRp) & Complete remission with incomplete hematologic recovery (CRi)], was defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extra-medullary blast foci as per Revised International Working Group (IWG) criteria.
Participants were classified as:
CRi, if they fulfilled all the criteria for CR except for incomplete hematological recovery with residual neutropenia < 1 × 10^9/L with or without complete platelet recovery. RBC and platelet transfusion independence was not required.
CRp, if they achieved CR except for incomplete platelet recovery (< 100 × 10^9/L).

RFS was estimated using Kaplan-Meier estimates. 99999 denotes upper limit was not estimable due to low number of events.

End point type	Primary

End point timeframe:

From the date of randomization until the date of documented relapse, or death; (Median time on study drug was 427 days for gilteritinib group and 212 days for placebo group)

The full analysis set (FAS) consisted of all participants who were randomized.

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	35		
Units: Months				
median (confidence interval 95%)	24.02 (14.06 to 99999)	15.84 (3.02 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Gilteritinib
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.163 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.738
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.407
upper limit	1.336

Notes:

[1] - Hazard ratio (HR), Cox proportional hazards model (CHM)

[2] - HR & 95% CI are based on CHM. Assuming proportional hazards, HR < 1 indicates a reduction in hazard rate in favor of gilteritinib arm. Stratification factors:age, geographic region, presence of MRD at screening, use of FLT3 inhibiting agents per IRT.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization until the date of death from any cause. OS was estimated using Kaplan-Meiers method.

Analysis Population: FAS Population

99999 denotes median and upper limit were not estimable due to low number of events.

End point type	Secondary

End point timeframe:

From the date of randomization until the date of death from any cause; (Median time on study drug was 427 days for gilteritinib group and 212 days for placebo group)

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	35		
Units: Months				
median (confidence interval 95%)	99999 (30.42 to 99999)	99999 (43.56 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	2.364

Notes:

[3] - HR & 95%CI are based on CHM. Assuming proportional hazards, HR < 1 indicates a reduction in hazard rate in favor of gilteritinib arm. Stratification factors:age, geographic region, presence of MRD at screening, use of FLT3 inhibiting agents per IRT.

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

EFS was defined as the time from the date of randomization until the date of documented relapse or discontinuation of the treatment, or initiation of other anti-leukemic treatment or death from any cause, whichever occurred first. Relapse after CR (including CRp and CRi), was defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extra-medullary blast foci as per Revised IWG criteria.

Participants were classified as:
CRi, if they fulfilled all the criteria for CR except for incomplete hematological recovery with residual neutropenia < 1 × 10^9/L with or without complete platelet recovery. RBC and platelet transfusion independence was not required.

CRp, if they achieved CR except for incomplete platelet recovery (< 100 × 10^9/L).

EFS was estimated using Kaplan-Meier's method.

Analysis Population: FAS Population

End point type	Secondary

End point timeframe:

From date of randomization until the date of documented relapse or discontinuation of the treatment, or initiation of other anti-leukemic treatment or death from any cause; (Median time on study drug was 427 days for gilteritinib and 212 days for placebo)

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	35		
Units: Months				
median (confidence interval 95%)	14.06 (9.89 to 23.72)	6.74 (2.86 to 21.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.296 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.862
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.455

Notes:

[4] - HR & 95%CI are based on CHM. Assuming proportional hazards, HR < 1 indicates a reduction in hazard rate in favor of gilteritinib arm. Stratification factors: age, geographic region, presence of MRD at screening, use of FLT3 inhibiting agents per IRT.

Secondary: Change from Baseline in Quantitative Minimal Residual Disease Measured as Log10-transformed Overall FLT3/ITD Mutation Ratio at Months 3, 6, 12, 24/End of Treatment (EoT)

End point title	Change from Baseline in Quantitative Minimal Residual Disease Measured as Log10-transformed Overall FLT3/ITD Mutation Ratio at Months 3, 6, 12, 24/End of Treatment (EoT)

End point description:

MRD was measured from bone marrow samples. FLT3/ITD mutation ratio was measured in relation to total FLT3. For a participant with multiple ITD mutations, the overall FLT3/ITD mutation ratio was calculated from the sum of all ITD mutations.

Analysis Population: FAS population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline and months 3, 6, 12, 24/EoT

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	22		
Units: Ratio				
arithmetic mean (standard deviation)				
Month 3 (n = 48, 22)	0.14 (± 0.96)	0.14 (± 1.46)		
Month 6 (n = 44, 17)	0.07 (± 0.92)	-0.17 (± 0.79)		
Month 12 (n = 32, 14)	-0.11 (± 0.60)	-0.34 (± 0.67)		
Month 24/EoT (n = 28, 14)	-0.12 (± 1.08)	0.23 (± 1.63)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Month 3

Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [5]
Method	ANCOVA

Notes:

[5] - 2-sided P-value from analysis of covariance (ANCOVA) including treatment, age group, geographic region and use of FLT3-inhibiting agents per IRT as fixed factors and baseline score as covariate.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Month 6

Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.415 [6]
Method	ANCOVA

Notes:

[6] - 2-sided P-value from ANCOVA including treatment, age group, geographic region and use of FLT3-inhibiting agents per IRT as fixed factors and baseline score as covariate.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Month 12

Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.271 [7]
Method	ANCOVA

Notes:

[7] - 2-sided P-value from ANCOVA including treatment, age group, geographic region and use of FLT3-inhibiting agents per IRT as fixed factors and baseline score as covariate.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Month 24/EoT

Comparison groups	Gilteritinib v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.179 [8]
Method	ANCOVA

Notes:

[8] - 2-sided P-value from ANCOVA including treatment, age group, geographic region and use of FLT3-inhibiting agents per IRT as fixed factors and baseline score as covariate.

Secondary: Number of Participants With Adverse Events (AE)

End point title	Number of Participants With Adverse Events (AE)

End point description:

AE:any untoward medical occurrence in participants administered study treatment (ST)/had undergone study procedures & did not necessarily have a causal relationship with treatment. Abnormalities was defined as AE only if met 1 of the criteria:Induced clinical signs/symptoms, required active intervention, required interruption or discontinuation of ST, abnormality or investigational value was clinically significant. Serious AE:resulted in death, was life threatening, persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions, congenital anomaly/birth defect, required hospitalization or prolongation of hospitalization, other medically important events. Treatment-emergent AE:recorded on treatment ≤ 30 days from last ST. Relapse: defined in Outcome Measure #1. Grades(Gr) based on National Cancer Institute Common Terminology Criteria (NCI-CTCAE) (Gr 1=mild, Gr 2=moderate, Gr 3 =severe, Gr 4 =life threatening, Gr 5 =death).

End point type	Secondary

End point timeframe:

From first dose date up to 30 days after last dose or data cut-off date 25-May 2021 (Maximum treatment duration was 744 days)

The safety analysis set (SAF) consisted of all randomized participants who received at least one dose of study drug.

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: Participants				
TEAE	58	33		
Drug-Related TEAE	51	20		
TEAE before Relapse	57	28		
Drug-Related TEAE before Relapse	51	15		
Serious TEAE	24	14		
Drug-Related Serious TEAE	10	3		
TEAE Leading to Death	1	1		
Drug-Related TEAE Leading to Death	0	1		
TEAE Leading to Withdrawal of Treatment	15	6		
Drug-Related TEAE Leading to Treatment Withdrawal	5	2		
TEAE Leading to Dose Reduction	15	1		
Drug-Related TEAE Leading to Dose Reduction	14	1		
TEAE Leading to Dose Interruption	35	4		
Drug-Related TEAE Leading to Dose Interruption	31	1		
Grade 3 or Higher TEAE	42	18		
Grade 3 or Higher Drug-related TEAE	33	4		
Death	20	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Eastern Cooperative Oncology Group

(ECOG) Performance Status Score

End point title	Number of Participants With Eastern Cooperative Oncology Group (ECOG) Performance Status Score

End point description:

ECOG performance status was measured on an 6 point scale.
0-Fully active, able to carry on all pre-disease performance without restriction.
1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5-Dead. Number of participants with ECOG PS was reported. ECOG PS grades with zero participants were not reported.

Analysis Population: Safety population with available data at specified time point.

End point type	Secondary

End point timeframe:

Baseline, months 2, 3, 4, 5, 6, 8, 10. 12, 14, 16, 18, 20, 22 and 24/EoT

End point values	Gilteritinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	35		
Units: Participants				
Baseline: Grade 0 (n = 62, 35)	39	22		
Baseline: Grade 1 (n = 62, 35)	23	13		
Month 2: Grade 0 (n = 54, 28)	38	18		
Month 2: Grade 1 (n = 54, 28)	16	9		
Month 2: Grade 2 (n = 54, 28)	0	1		
Month 3: Grade 0 (n = 52, 25)	33	20		
Month 3: Grade 1 (n = 52, 25)	19	4		
Month 3: Grade 2 (n = 52, 25)	0	1		
Month 4: Grade 0 (n = 49, 22)	37	16		
Month 4: Grade 1 (n = 49, 22)	12	6		
Month 5: Grade 0 (n = 46, 21)	35	17		
Month 5: Grade 1 (n = 46, 21)	11	4		
Month 6: Grade 0 (n = 43, 19)	32	17		
Month 6: Grade 1 (n = 43, 19)	11	2		
Month 8: Grade 0 (n = 41, 18)	32	12		
Month 8: Grade 1 (n = 41, 18)	8	6		
Month 8: Grade 2 (n = 41, 18)	1	0		
Month 10: Grade 0 (n = 37, 17)	29	14		
Month 10: Grade 1 (n = 37, 17)	8	3		
Month 12: Grade 0 (n= 35, 17)	24	14		
Month 12: Grade 1 (n= 35, 17)	11	3		
Month 14: Grade 0 (n = 30, 16)	21	13		
Month 14: Grade 1 (n = 30, 16)	9	3		
Month 16: Grade 0 (n = 28, 13)	22	11		
Month 16: Grade 1 (n = 28, 13)	4	2		
Month 16: Grade 2 (n = 28, 13)	2	0		
Month 18: Grade 0 (n = 27, 14)	19	13		

Month 18: Grade 1 (n = 27, 14)	8	1		
Month 20: Grade 0 (n = 25, 14)	18	13		
Month 20: Grade 1 (n = 25, 14)	7	1		
Month 22: Grade 0 (n = 24, 13)	20	11		
Month 22: Grade 1 (n = 24, 13)	4	2		
Month 24/EoT: Grade 0 (n = 51, 28)	34	20		
Month 24/EoT: Grade 1 (n = 51, 28)	14	6		
Month 24/EoT: Grade 2 (n = 51, 28)	1	0		
Month 24/EoT: Grade 3 (n = 51, 28)	1	1		
Month 24/EoT: Grade 4 (n = 51, 28)	1	1		

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 last dose or data cut-off date 25-May-2021 (Maximum treatment duration was 744 days)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

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

Reporting group title	Gilteritinib

Reporting group description:

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

Serious adverse events	Placebo	Gilteritinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 35 (40.00%)	24 / 62 (38.71%)	
number of deaths (all causes)	11	20	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia recurrent			
subjects affected / exposed	5 / 35 (14.29%)	7 / 62 (11.29%)	
occurrences causally related to treatment / all	1 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chloroma			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			

subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia recurrent			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mastocytosis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thymoma			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Neurogenic shock			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (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	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			

subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epilepsy			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 62 (3.23%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperleukocytosis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Anal haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (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 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (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			
Back pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			

subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 35 (2.86%)	0 / 62 (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			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Gilteritinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 35 (91.43%)	53 / 62 (85.48%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 35 (8.57%)	10 / 62 (16.13%)	
occurrences (all)	4	10	
Malaise			
subjects affected / exposed	3 / 35 (8.57%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Oedema peripheral			
subjects affected / exposed	4 / 35 (11.43%)	3 / 62 (4.84%)	
occurrences (all)	4	3	
Pyrexia			
subjects affected / exposed	3 / 35 (8.57%)	3 / 62 (4.84%)	
occurrences (all)	4	3	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	2 / 35 (5.71%)	2 / 62 (3.23%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 35 (5.71%)	9 / 62 (14.52%)	
occurrences (all)	2	12	
Dyspnoea			
subjects affected / exposed	2 / 35 (5.71%)	4 / 62 (6.45%)	
occurrences (all)	2	5	
Epistaxis			

subjects affected / exposed	1 / 35 (2.86%)	4 / 62 (6.45%)	
occurrences (all)	1	5	
Oropharyngeal pain			
subjects affected / exposed	2 / 35 (5.71%)	1 / 62 (1.61%)	
occurrences (all)	2	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 35 (5.71%)	4 / 62 (6.45%)	
occurrences (all)	2	5	
Restlessness			
subjects affected / exposed	2 / 35 (5.71%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	8 / 62 (12.90%)	
occurrences (all)	3	17	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 35 (2.86%)	7 / 62 (11.29%)	
occurrences (all)	1	12	
Blood bilirubin increased			
subjects affected / exposed	2 / 35 (5.71%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 35 (2.86%)	18 / 62 (29.03%)	
occurrences (all)	1	37	
Blood creatinine increased			
subjects affected / exposed	1 / 35 (2.86%)	5 / 62 (8.06%)	
occurrences (all)	2	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 35 (0.00%)	7 / 62 (11.29%)	
occurrences (all)	0	7	
Neutrophil count decreased			
subjects affected / exposed	3 / 35 (8.57%)	12 / 62 (19.35%)	
occurrences (all)	5	46	
Platelet count decreased			

subjects affected / exposed	4 / 35 (11.43%)	12 / 62 (19.35%)	
occurrences (all)	10	24	
Weight increased			
subjects affected / exposed	2 / 35 (5.71%)	8 / 62 (12.90%)	
occurrences (all)	4	11	
White blood cell count decreased			
subjects affected / exposed	3 / 35 (8.57%)	6 / 62 (9.68%)	
occurrences (all)	3	24	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 35 (8.57%)	1 / 62 (1.61%)	
occurrences (all)	3	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 35 (11.43%)	8 / 62 (12.90%)	
occurrences (all)	4	9	
Headache			
subjects affected / exposed	1 / 35 (2.86%)	5 / 62 (8.06%)	
occurrences (all)	1	9	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 35 (14.29%)	5 / 62 (8.06%)	
occurrences (all)	8	8	
Leukopenia			
subjects affected / exposed	1 / 35 (2.86%)	7 / 62 (11.29%)	
occurrences (all)	1	8	
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	10 / 62 (16.13%)	
occurrences (all)	1	32	
Thrombocytopenia			
subjects affected / exposed	4 / 35 (11.43%)	11 / 62 (17.74%)	
occurrences (all)	4	17	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 35 (2.86%)	5 / 62 (8.06%)	
occurrences (all)	1	5	

Eye disorders			
Dry eye			
subjects affected / exposed	2 / 35 (5.71%)	5 / 62 (8.06%)	
occurrences (all)	2	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 35 (2.86%)	7 / 62 (11.29%)	
occurrences (all)	1	8	
Diarrhoea			
subjects affected / exposed	3 / 35 (8.57%)	5 / 62 (8.06%)	
occurrences (all)	3	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 35 (5.71%)	4 / 62 (6.45%)	
occurrences (all)	3	4	
Nausea			
subjects affected / exposed	7 / 35 (20.00%)	8 / 62 (12.90%)	
occurrences (all)	7	10	
Stomatitis			
subjects affected / exposed	3 / 35 (8.57%)	3 / 62 (4.84%)	
occurrences (all)	3	3	
Vomiting			
subjects affected / exposed	2 / 35 (5.71%)	2 / 62 (3.23%)	
occurrences (all)	2	3	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 35 (2.86%)	4 / 62 (6.45%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 35 (5.71%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	2 / 35 (5.71%)	6 / 62 (9.68%)	
occurrences (all)	2	6	
Rash			
subjects affected / exposed	3 / 35 (8.57%)	3 / 62 (4.84%)	
occurrences (all)	4	3	

Skin lesion			
subjects affected / exposed	2 / 35 (5.71%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 35 (8.57%)	4 / 62 (6.45%)	
occurrences (all)	3	6	
Back pain			
subjects affected / exposed	4 / 35 (11.43%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Bone pain			
subjects affected / exposed	2 / 35 (5.71%)	0 / 62 (0.00%)	
occurrences (all)	2	0	
Pain in extremity			
subjects affected / exposed	1 / 35 (2.86%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 35 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Herpes zoster			
subjects affected / exposed	2 / 35 (5.71%)	1 / 62 (1.61%)	
occurrences (all)	2	2	
Influenza			
subjects affected / exposed	2 / 35 (5.71%)	1 / 62 (1.61%)	
occurrences (all)	2	1	
Nasopharyngitis			
subjects affected / exposed	6 / 35 (17.14%)	7 / 62 (11.29%)	
occurrences (all)	11	11	
Upper respiratory tract infection			
subjects affected / exposed	2 / 35 (5.71%)	3 / 62 (4.84%)	
occurrences (all)	3	3	
Otitis media			
subjects affected / exposed	2 / 35 (5.71%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			

subjects affected / exposed	2 / 35 (5.71%)	3 / 62 (4.84%)	
occurrences (all)	2	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 35 (8.57%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Hyperglycaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 62 (0.00%)	
occurrences (all)	3	0	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 62 (3.23%)	
occurrences (all)	5	7	
Hyperuricaemia			
subjects affected / exposed	1 / 35 (2.86%)	4 / 62 (6.45%)	
occurrences (all)	1	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2017	The changes included: Add requirement for central hematology assessment during the first month on treatment at Days 1, 8, 15 & 29, as well as during all regularly scheduled visits beginning at Month 2. To collect hematology assessments at all the same times as other routine laboratory assessments to ensure identification of relapse at the earliest time point.
25 April 2019	The changes included: The study is changed from a phase 3 to phase 2. Prior text indicating target numbers for enrollment based on an adaptive design is modified to remove the adaptive design element and provide approximate enrollment numbers moving forward. The interim analysis that was originally planned is removed. Inclusion criterion 3 makes note of a diagnostic test that was previously under development but is now available. The revision reflects this change in the diagnostic test status. The duration of treatment no longer includes the requirement for a 3-year follow-up (to start after the 30-day follow-up) or for 80% of the subjects to have a relapse-free survival (RFS) event, whichever comes first. The primary analysis hypothesis test on the primary endpoint of RFS is changed from the Wald test based on stratified Cox-proportional hazards model to a stratified log-rank test, and the stratified Cox-proportional hazards model is then used as sensitivity analysis. A weighted statistics model (CHW method) will no longer be applied to the primary endpoint analysis. Language is added to clarify the conditions under which unblinding could occur, including in the event of documented relapse.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported