Clinical trial results:
A phase III, randomized, double-blind study of chemotherapy with daunorubicin or idarubicin and cytarabine for Induction and intermediate dose cytarabine for consolidation plus midostaurin (PKC412) or chemotherapy plus placebo in newly diagnosed subjects with FLT-3 mutation negative acute myeloid leukemia (AML)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate.

Summary

EudraCT number	2017-003540-21
Trial protocol	DE BE IT PT FR NO ES AT HU BG PL
Global end of trial date	12 February 2021

Results information

Result version number	v1
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	CPKC412E2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02913261
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, novartis.email@novartis.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine if the addition of midostaurin to standard induction and consolidation therapy, followed by single agent post-consolidation therapy improves event free survival (EFS) in subjects with newly diagnosed FLT3-MN (signal ratio (SR) <0.05) AML.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 165
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 79
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Norway: 7
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 11

Country: Number of subjects enrolled	Spain: 63
Country: Number of subjects enrolled	Switzerland: 17
Country: Number of subjects enrolled	Taiwan: 11
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	501
EEA total number of subjects	396

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)	358
From 65 to 84 years	143
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Five hundred and three participants were randomized. However, the data analysis was considered for 501 participants only (250 participants in midostaurin arm and 251 participants in placebo arm).

Pre-assignment

Screening details:

Participants had to sign informed consent form before screening for enrollment. Participants started chemotherapy at day 1 and were randomized at day 8.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Midostaurin + chemotherapy

Arm description:

Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

Arm type	Experimental
Investigational medicinal product name	Midostaurin
Investigational medicinal product code	PKC412
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

50 mg twice daily

Investigational medicinal product name	Chemotherapy: daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg/m^2/d, day 1 -3 (induction 1), 50 mg/m^2/d, day 1 -3 (induction 2)

Investigational medicinal product name	Chemotherapy: cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m^2/d, days 1 -7 (induction 1), 1.5 g/m^2/day, q12h, day 1 -3 (induction 2 & Consolidation)

Investigational medicinal product name	Chemotherapy: idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg/m^2/d, day 1 -3 (induction 1), 10 mg/m^2/d, day 1 -3 (induction 2)

Arm title	Placebo + chemotherapy

Arm description:

Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.

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

Dosage and administration details:

50 mg twice daily

Investigational medicinal product name	Chemotherapy: daunorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

60 mg/m^2/d, day 1 -3 (induction 1), 50 mg/m^2/d, day 1 -3 (induction 2)

Investigational medicinal product name	Chemotherapy: cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m^2/d, days 1 -7 (induction 1), 1.5 g/m^2/day, q12h, day 1 -3 (induction 2 & Consolidation)

Investigational medicinal product name	Chemotherapy: idarubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg/m^2/d, day 1 -3 (induction 1), 10 mg/m^2/d, day 1 -3 (induction 2)

Number of subjects in period 1	Midostaurin + chemotherapy	Placebo + chemotherapy
Started	250	251
Treated with Midostaurin/Placebo	245	249
Completed	2	1
Not completed	248	250

Adverse event, serious fatal	14	9
Physician decision	60	60
Terminated by Sponsored	46	50
Subject Decision	15	12
Adverse event, non-fatal	30	34
Failure to meet Continuation Criteria	24	28
Withdrawal of informed consent	20	14
Missing	3	13
Guardian decision	1	1
Lack of efficacy	19	11
New Therapy for Study Indication	16	16
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Midostaurin + chemotherapy
Reporting group description:	
Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Reporting group title	Placebo + chemotherapy
Reporting group description:	
Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	

Reporting group values	Midostaurin + chemotherapy	Placebo + chemotherapy	Total
Number of subjects	250	251	501
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	182	176	358
From 65-84 years	68	75	143
85 years and over	0	0	0
Age Continuous Units: Years			
median	58.0	58.0	
full range (min-max)	19.0 to 78.0	18.0 to 79.0	-
Sex: Female, Male Units: Participants			
Female	122	106	228
Male	128	145	273
Race/Ethnicity, Customized Units: Subjects			
White	213	208	421
Black or African American	1	2	3
Asian	22	22	44
Multiple	1	1	2
Missing	13	18	31
ECOG performance status Units: Subjects			
0 Status	119	119	238

1 Status	107	115	222
2 Status	18	13	31
3 Status	2	0	2
Missing Status	4	4	8

End points

End points reporting groups

Reporting group title	Midostaurin + chemotherapy
Reporting group description:	
Participants received Midostaurin in Induction 50mg twice daily on Day 8 until 48 hrs before start of next cycle. During Induction 2 and consolidation 50mg twice daily on Day 4 until 48 hrs before start of next cycle. During post-consolidation 50mg twice daily for 28 consecutive days of each 28-day treatment cycle up to 12 cycles. For participants who could not tolerate the protocol-specified dosing schedule, dose interruptions and/or reductions were either recommended or mandated allowing participants to continue the study treatment. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Reporting group title	Placebo + chemotherapy
Reporting group description:	
Participants received matching placebo to midostaurin with same dose, plus chemotherapy. Chemotherapy consisted of daunorubicin or idarubicin and cytarabine for induction and intermediate dose cytarabine for consolidation.	
Subject analysis set title	CGP52421
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Active Midostaurin metabolite	
Subject analysis set title	CGP62221
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Active Midostaurin metabolite	
Subject analysis set title	CGP52421
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Active Midostaurin metabolite	
Subject analysis set title	CGP62221
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Active Midostaurin metabolite	
Subject analysis set title	GCP62221
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Active Midostaurin metabolite	
Subject analysis set title	GCP52421
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Active Midostaurin metabolite	

Primary: Event Free Survival (EFS)

End point title	Event Free Survival (EFS)
End point description:	
EFS was defined as the time from randomization to failure to obtain a complete remission (CR) or Complete remission with incomplete hematologic recovery (CRi) with adequate blood count recovery in induction, relapse after CR or CRi with adequate blood countrecovery or death due to any cause, whichever occurred first as assessed by the investigator.	
End point type	Primary
End point timeframe:	
From date of Randomization up to approx. 30 months	

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Months				
median (confidence interval 95%)	5.98 (2.33 to 8.97)	5.88 (3.65 to 7.52)		

Statistical analyses

Statistical analysis title	for EFS
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.0239
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.31

Secondary: Overall survival (OS) (Key Secondary)

End point title	Overall survival (OS) (Key Secondary)

End point description:

OS was defined as the time from randomization to date of death due to any cause. Patients entered the survival follow-up phase once they completed the safety follow up period (30 days after the last dose of midostaurin/placebo) in case of induction failure or if they had relapsed during post-treatment follow-up. Patients were then contacted by telephone every 3 months +/- 2 weeks or had a visit to follow up on their survival status, per Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

Between randomization to date of death up to approx. 30 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Months				
median (confidence interval 95%)	99 (15.54 to 999)	19.22 (13.8 to 999)		

Statistical analyses

Statistical analysis title	For OS
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8728
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.29

Secondary: Percentage of participants with complete remission (CR) and complete remission with incomplete hematological recovery (CRi) but with adequate blood count recovery rate.

End point title	Percentage of participants with complete remission (CR) and complete remission with incomplete hematological recovery (CRi) but with adequate blood count recovery rate.

End point description:

Assessment was based on the International Working Group (IWG) criteria for AML as per investigator assessment.
CR: Bone marrow: < 5% blasts
no blasts with Auer rods; Peripheral blood: neutrophils ≥ 1.0 x 109/L
platelets ≥ 100 x 109/L, no blasts; No evidence of extramedullary disease (such as central nervous system (CNS) or soft tissue involvement); Transfusion independent.
CRi with adequate blood count recovery is defined as the following:
Bone marrow
< 5% blasts
no blasts with Auer rods
Peripheral blood
Neutrophils >= 1.0 x 109/L and 50 x 109/L <=platelets < 100 x 109/L
no blasts
No evidence of extramedullary disease (such as CNS or soft tissue involvement).

End point type	Secondary

End point timeframe:

At maximum 93 days from induction therapy start

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Percentage of participants				
number (confidence interval 95%)	59.2 (52.8 to 65.4)	61.0 (54.6 to 67.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Minimal Residual Disease (MRD) negative status

End point title	Percentage of participants with Minimal Residual Disease (MRD) negative status

End point description:

Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP).
MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.

End point type	Secondary

End point timeframe:

Between start and three months after end of treatment

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Percentage of participants				
number (not applicable)	40.8	41.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Minimal Residual Disease (MRD) negative status during Post-consolidation Phase

End point title	Percentage of participants with Minimal Residual Disease (MRD) negative status during Post-consolidation Phase

End point description:

MRD- rate was defined as the rate of participants reaching MRD at any timepoint during Post-consolidation phase. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP).
MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.

End point type	Secondary

End point timeframe:

Between start and three months after end of treatment

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	27		
Units: Percentage of participants				
number (not applicable)	33.3	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Measurable Residual Disease (MRD) negativity by flow cytometry

End point title	Time to Measurable Residual Disease (MRD) negativity by flow cytometry

End point description:

Time to MRD- is defined as time from randomization to first occurrence of MRD-. Participants with leukemic blasts below 0.1% were considered as MRD-negative based on leukemia-associated immunophenotype (LAIP).
MRD was derived from bone marrow and blood data using cellular and molecular technologies and MRD status was measured using the flow cytometry assessments for LAIP irrespective of the investigator's overall clinical response assessment.

End point type	Secondary

End point timeframe:

From date of Randomization up to approx. 17 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Days				
median (confidence interval 95%)	2.27 (1.61 to 5.68)	2.07 (1.68 to 6.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free survival (DFS)

End point title	Disease-free survival (DFS)

End point description:

DFS as measured from the date of first CR or CRi with adequate blood count recovery to relapse or death due to any cause, whichever occurred first. Participants who did not relapse nor die were censored at the last adequate response assessment. Assessment was based on the IWG criteria for AML as per investigator assessment

End point type	Secondary

End point timeframe:

From date of CR or CRi with adequate blood count recovery up to approx. 30 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	153		
Units: Months				
median (confidence interval 95%)	10.5 (7.59 to 99)	9.1 (6.87 to 12.02)		

Statistical analyses

Statistical analysis title	For DFS
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.63

Secondary: Cumulative incidence of relapse (CIR)

End point title	Cumulative incidence of relapse (CIR)

End point description:

Cumulative Incidence of Relapse (CIR) was defined for participants with CR or CRi with adequate blood count recovery and was the time from achieving the CR or CRi with adequate blood count recovery until the onset of relapse from CR or CRi with adequate blood recovery. Participants without relapse were censored at the last adequate response assessment. Participants who died without relapse were counted as a competing cause of failure.

End point type	Secondary

End point timeframe:

From date of CR or CRi with adequate blood count recovery up to approx. 30 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	153		
Units: Months				
median (confidence interval 95%)	5.1 (2.83 to 7.56)	6.6 (4.99 to 8.77)		

Statistical analyses

Statistical analysis title	For CIR
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5866
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.87

Secondary: Cumulative incidence of death (CID)

End point title	Cumulative incidence of death (CID)

End point description:

Cumulative Incidence of Death (CID) was defined for all participants achieving CR or CRi with adequate blood count recovery measured from the date of achievement of CR or CRi until the date of death due to any reason. Participants not known to have died were censored on the last contact date. Participants who experienced relapse were counted as a competing cause of failure.

End point type	Secondary

End point timeframe:

From date of CR or CRi with adequate blood count recovery up to approx. 30 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	148	153		
Units: Months				
median (confidence interval 95%)	99 (18.00 to 999)	99 (14.42 to 999)		

Statistical analyses

Statistical analysis title	For CID
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7937
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.54

Secondary: Time to CR or CRi with adequate blood count recovery

End point title	Time to CR or CRi with adequate blood count recovery

End point description:

Time to CR or CRi with adequate blood count recovery was defined as the time from randomization to CR or CRi with adequate blood count recovery whichever occurred first

End point type	Secondary

End point timeframe:

At maximum 93 days from induction therapy start

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Days				
median (confidence interval 95%)	1.12 (1.02 to 1.41)	1.15 (1.05 to 1.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to partial and full neutrophil recovery

End point title	Time to partial and full neutrophil recovery

End point description:

The time to neutrophil recovery was assessed for the following criteria: number of days from start of treatment to the first day neutrophils ≥0.5 x 10^9/L, Number of days from start of treatment to the first day neutrophils ≥1.0 x 10^9/L

End point type	Secondary

End point timeframe:

At maximum 93 days from induction therapy start

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Months				
median (confidence interval 95%)				
Partial neutrophil recovery	1.1 (0.82 to 1.15)	0.9 (0.79 to 1.12)		
Full neutrophil recovery	1.2 (1.05 to 1.48)	1.1 (0.95 to 1.35)		

Statistical analyses

Statistical analysis title	For neutrophil recovery - Pbo
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.14

Statistical analysis title	For neutrophil recovery
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.16

Secondary: Time to partial and full platelet recovery	
End point title	Time to partial and full platelet recovery

End point description:

Time to platelet recovery was assessed for the following criteria: number of days from start of treatment to the first day platelets ≥50 x 10^9/L (partial platelet recovery), number of days from start of treatment to the first day platelets ≥100 x 10^9/L (full platelet recovery).

End point type	Secondary

End point timeframe:

At maximum 93 days from induction therapy start

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Months				
median (confidence interval 95%)				
Partial platelet recovery	99 (1.45 to 999)	99 (3.5 to 999)		
Full platelet recovery	0.953 (0.89 to 1.12)	0.887 (0.85 to 0.92)		

Statistical analyses

Statistical analysis title	For platelet recovery
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.52

Statistical analysis title	For platelet recovery - Pbo
Comparison groups	Midostaurin + chemotherapy v Placebo + chemotherapy
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1

Secondary: AUC0-t: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

End point title	AUC0-t: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221[1]

End point description:

The AUC from time zero to a measurable concentration sampling time (t) (mass x time x volume-1).
Note: as the last sampling time was at 12 h, AUC0-12h was determined after the first dose, reported at Cycle 1, Day 8

End point type	Secondary

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[1] - 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: No statistical analysis was planned for this endpoint

End point values	Midostaurin + chemotherapy	CGP52421	CGP62221	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	27	27	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	14800 (± 37.5)	712 (± 78.4)	1830 (± 135)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations for midostaurin and its metabolites: CGP52421 and CGP62221

End point title	Plasma concentrations for midostaurin and its metabolites: CGP52421 and CGP62221[2]

End point description:

Serial pharmacokinetics (PK) samples were collected in all participants to assess the plasma concentrations of midostaurin, CGP52421 and CGP622.
Plasma concentrations of midostaurin and its active metabolites CGP62221 and CGP52421 were measured using a validated liquid chromatography-tandem mass spectrometry (LC- MS/MS) assay and reported at Cycle 1, Day 8

End point type	Secondary

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[2] - 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: No statistical analysis was planned for this endpoint

End point values	Midostaurin + chemotherapy	CGP52421	CGP62221	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: ng/mL				

Notes:

[3] - Plasma concentrations for serial PK samples not calculated.They cannot be reported as a single value
[4] - Plasma concentrations for serial PK samples not calculated.They cannot be reported as a single value
[5] - Plasma concentrations for serial PK samples not calculated.They cannot be reported as a single value

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

End point title	AUClast: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221[6]

End point description:

The AUC from time zero to the last measurable concentration sampling time after the first dose reported at Cycle 1, Day 8

End point type	Secondary

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[6] - 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: No statistical analysis was planned for this endpoint

End point values	Midostaurin + chemotherapy	CGP52421	CGP62221	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	27	27	
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	12200 (± 59.6)	493 (± 139)	1130 (± 249)	

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

End point title	Cmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221[7]

End point description:

The maximum (peak) observed plasma drug concentration after the first dose administration reported at Cycle 1, Day 8

End point type	Secondary

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[7] - 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: No statistical analysis was planned for this endpoint

End point values	Midostaurin + chemotherapy	CGP52421	GCP62221	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	27	27	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1910 (± 37.8)	74.7 (± 72.3)	183 (± 128)	

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221

End point title	Tmax: Pharmacokinetic (PK) parameter for midostaurin and its metabolites: CGP52421 and CGP62221[8]

End point description:

The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration reported at Cycle 1, Day 8

End point type	Secondary

End point timeframe:

Pre-dose, 1hr, Post-dose 3hrs +/- 0.5hrs, 6hrs, 12 hrs

Notes:

[8] - 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: No statistical analysis was planned for this endpoint

End point values	Midostaurin + chemotherapy	CGP62221	GCP52421	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	27	27	
Units: hour (hr)				
geometric mean (geometric coefficient of variation)	3.28 (± 101)	7.17 (± 57.8)	5.38 (± 89.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Total score for each time point for the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)

End point title	Total score for each time point for the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)

End point description:

The total FACT-Leu score consists of 44 items with total scores ranging from 0 to 176. Higher scores indicate better HRQoL. Negative changes from baseline indicate a worsening of HRQoL while positive changes indicate an improvement in HRQoL.

End point type	Secondary

End point timeframe:

From date of Randomization up to approx. 18 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n = 225, 223)	122.8 (± 22.64)	123.1 (± 21.21)		
Induction Phase (n = 137, 147)	123.9 (± 21.50)	122.1 (± 19.51)		
Induction I (n = 105, 90)	124.8 (± 20.34)	123.5 (± 20.28)		
Induction ll (n = 32, 57)	121.0 (± 25.09)	119.8 (± 18.15)		
Consolidation (prior) (n = 210, 196)	135.9 (± 17.67)	136.9 (± 21.03)		
Post- consolidation (n = 169, 114)	143.7 (± 21.45)	140.1 (± 21.60)		
Follow-up (n = 74, 111)	136.4 (± 22.87)	139.2 (± 25.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Scores for each time point for the EQ5D-5L (a visual analogue scale (VAS))

End point title	Scores for each time point for the EQ5D-5L (a visual analogue scale (VAS))

End point description:

The EQ5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflect increasing levels of difficulty. The patient is asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also included a Visual Analogue Scale (VAS), where the patient is asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

End point type	Secondary

End point timeframe:

From date of Randomization up to approx. 18 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline (n= 225, 220)	62.7 (± 22.98)	64.3 (± 22.15)		
Induction Phase (n = 135, 146)	67.9 (± 20.95)	64.4 (± 21.29)		
Induction I (n = 104, 89)	68.1 (± 21.02)	64.0 (± 21.92)		
Induction II (n = 31, 57)	66.9 (± 21.03)	65.2 (± 20.44)		
Consolidation (prior) (n = 207, 197)	79.1 (± 15.42)	76.2 (± 16.37)		
Post-consolidation (n = 167, 113)	83.9 (± 15.00)	77.3 (± 14.92)		
Follow-up (n- 74, 112)	74.3 (± 20.08)	73.4 (± 1972)		

Statistical analyses

No statistical analyses for this end point

Secondary: All Collected Deaths

End point title	All Collected Deaths

End point description:

On-treatment deaths were collected from start of treatment (FPFT) up to 30 days after study drug discontinuation, for a maximum duration of approx. 18 months.

Deaths post-treatment survival follow up were collected after the on-treatment period up to approx. 18 months. Participants who did not die during the on-treatment period and had not stopped study participation at the time of data cut-off (when study was terminated) were censored.

End point type	Secondary

End point timeframe:

Start of study treatment up to 30 days post-treatment for approx. 1 year, prior to study treatment up to LPLV, approx. 18 months

End point values	Midostaurin + chemotherapy	Placebo + chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	251		
Units: Participants				
Total Deaths	46	53		
Deaths on-treatment	25	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from first dose of study treatment until end of treatment plus 30 days, up to a maximum duration of 573 days for midostaurin and up to a maximum duration of 416 days for Placebo

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Midostaurin

Reporting group description:

Midostaurin

Serious adverse events	Placebo	Midostaurin	
Total subjects affected by serious adverse events			
subjects affected / exposed	114 / 249 (45.78%)	95 / 245 (38.78%)	
number of deaths (all causes)	53	46	
number of deaths resulting from adverse events	4	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma recurrent			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chloroma			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
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			
Disease progression			
subjects affected / exposed	0 / 249 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 249 (1.61%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 4	2 / 2	
Mucosal inflammation			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 249 (1.61%)	4 / 245 (1.63%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary toxicity			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 249 (2.41%)	4 / 245 (1.63%)	
occurrences causally related to treatment / all	3 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count increased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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 decreased			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary function test decreased			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
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	3 / 249 (1.20%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Expired product administered			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			

subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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			
Aplasia			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 249 (1.20%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial infarction			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
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 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			

subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial spasm			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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	1 / 249 (0.40%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	23 / 249 (9.24%)	16 / 245 (6.53%)	
occurrences causally related to treatment / all	12 / 32	10 / 24	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	2 / 249 (0.80%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jejunal stenosis			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Mechanical ileus			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	3 / 249 (1.20%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Oral dysaesthesia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative duodenitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 249 (0.80%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 249 (1.20%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity vasculitis			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyrotoxic crisis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytarabine syndrome			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acinetobacter infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess neck			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 249 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			

subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral fungal infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial sepsis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus colitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	2 / 249 (0.80%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	1 / 249 (0.40%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatosplenic candidiasis			
subjects affected / exposed	0 / 249 (0.00%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 249 (0.40%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pelvic abscess			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 249 (0.40%)	2 / 245 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	12 / 249 (4.82%)	9 / 245 (3.67%)	
occurrences causally related to treatment / all	3 / 12	6 / 9	
deaths causally related to treatment / all	2 / 3	1 / 1	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	13 / 249 (5.22%)	11 / 245 (4.49%)	
occurrences causally related to treatment / all	6 / 16	4 / 11	
deaths causally related to treatment / all	1 / 1	1 / 4	
Streptococcal infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	9 / 249 (3.61%)	8 / 245 (3.27%)	
occurrences causally related to treatment / all	1 / 9	1 / 8	
deaths causally related to treatment / all	0 / 4	0 / 3	
Streptococcal sepsis			
subjects affected / exposed	0 / 249 (0.00%)	3 / 245 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic mycosis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral myocarditis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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			
Decreased appetite			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (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	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 249 (0.00%)	1 / 245 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	2 / 249 (0.80%)	0 / 245 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Placebo	Midostaurin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	245 / 249 (98.39%)	242 / 245 (98.78%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 249 (10.84%)	20 / 245 (8.16%)	
occurrences (all)	32	25	
Hypotension			
subjects affected / exposed	25 / 249 (10.04%)	17 / 245 (6.94%)	
occurrences (all)	27	20	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 249 (6.02%)	17 / 245 (6.94%)	
occurrences (all)	20	22	
Chills			
subjects affected / exposed	11 / 249 (4.42%)	16 / 245 (6.53%)	
occurrences (all)	13	23	
Fatigue			
subjects affected / exposed	26 / 249 (10.44%)	36 / 245 (14.69%)	
occurrences (all)	32	44	
Mucosal inflammation			

subjects affected / exposed	50 / 249 (20.08%)	47 / 245 (19.18%)	
occurrences (all)	60	53	
Oedema			
subjects affected / exposed	21 / 249 (8.43%)	27 / 245 (11.02%)	
occurrences (all)	25	46	
Oedema peripheral			
subjects affected / exposed	38 / 249 (15.26%)	44 / 245 (17.96%)	
occurrences (all)	44	54	
Pain			
subjects affected / exposed	8 / 249 (3.21%)	15 / 245 (6.12%)	
occurrences (all)	9	17	
Pyrexia			
subjects affected / exposed	138 / 249 (55.42%)	146 / 245 (59.59%)	
occurrences (all)	284	308	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	37 / 249 (14.86%)	33 / 245 (13.47%)	
occurrences (all)	46	37	
Dyspnoea			
subjects affected / exposed	27 / 249 (10.84%)	28 / 245 (11.43%)	
occurrences (all)	35	44	
Epistaxis			
subjects affected / exposed	43 / 249 (17.27%)	44 / 245 (17.96%)	
occurrences (all)	57	58	
Oropharyngeal pain			
subjects affected / exposed	22 / 249 (8.84%)	17 / 245 (6.94%)	
occurrences (all)	25	23	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 249 (6.02%)	9 / 245 (3.67%)	
occurrences (all)	18	12	
Insomnia			
subjects affected / exposed	25 / 249 (10.04%)	16 / 245 (6.53%)	
occurrences (all)	29	18	
Investigations			

Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 249 (5.22%)	9 / 245 (3.67%)	
occurrences (all)	16	9	
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 249 (7.23%)	24 / 245 (9.80%)	
occurrences (all)	34	33	
Alanine aminotransferase increased			
subjects affected / exposed	29 / 249 (11.65%)	29 / 245 (11.84%)	
occurrences (all)	42	45	
Blood bilirubin increased			
subjects affected / exposed	7 / 249 (2.81%)	19 / 245 (7.76%)	
occurrences (all)	10	23	
C-reactive protein increased			
subjects affected / exposed	13 / 249 (5.22%)	15 / 245 (6.12%)	
occurrences (all)	19	19	
Electrocardiogram QT prolonged			
subjects affected / exposed	13 / 249 (5.22%)	26 / 245 (10.61%)	
occurrences (all)	14	32	
Gamma-glutamyltransferase increased			
subjects affected / exposed	26 / 249 (10.44%)	17 / 245 (6.94%)	
occurrences (all)	36	22	
Neutrophil count decreased			
subjects affected / exposed	20 / 249 (8.03%)	20 / 245 (8.16%)	
occurrences (all)	41	45	
Platelet count decreased			
subjects affected / exposed	50 / 249 (20.08%)	34 / 245 (13.88%)	
occurrences (all)	119	65	
White blood cell count decreased			
subjects affected / exposed	35 / 249 (14.06%)	25 / 245 (10.20%)	
occurrences (all)	76	45	
Weight increased			
subjects affected / exposed	24 / 249 (9.64%)	17 / 245 (6.94%)	
occurrences (all)	37	41	
Injury, poisoning and procedural complications			

Transfusion reaction			
subjects affected / exposed	11 / 249 (4.42%)	13 / 245 (5.31%)	
occurrences (all)	15	16	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	16 / 249 (6.43%)	14 / 245 (5.71%)	
occurrences (all)	17	15	
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 249 (9.24%)	14 / 245 (5.71%)	
occurrences (all)	36	15	
Headache			
subjects affected / exposed	64 / 249 (25.70%)	70 / 245 (28.57%)	
occurrences (all)	102	93	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	96 / 249 (38.55%)	77 / 245 (31.43%)	
occurrences (all)	251	166	
Febrile neutropenia			
subjects affected / exposed	116 / 249 (46.59%)	102 / 245 (41.63%)	
occurrences (all)	187	185	
Pancytopenia			
subjects affected / exposed	13 / 249 (5.22%)	6 / 245 (2.45%)	
occurrences (all)	27	17	
Thrombocytopenia			
subjects affected / exposed	69 / 249 (27.71%)	62 / 245 (25.31%)	
occurrences (all)	191	167	
Leukopenia			
subjects affected / exposed	31 / 249 (12.45%)	20 / 245 (8.16%)	
occurrences (all)	56	35	
Neutropenia			
subjects affected / exposed	53 / 249 (21.29%)	34 / 245 (13.88%)	
occurrences (all)	101	63	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	46 / 249 (18.47%)	41 / 245 (16.73%)	
occurrences (all)	54	46	

Abdominal pain upper			
subjects affected / exposed	34 / 249 (13.65%)	24 / 245 (9.80%)	
occurrences (all)	40	31	
Constipation			
subjects affected / exposed	84 / 249 (33.73%)	77 / 245 (31.43%)	
occurrences (all)	118	112	
Diarrhoea			
subjects affected / exposed	142 / 249 (57.03%)	121 / 245 (49.39%)	
occurrences (all)	210	185	
Dyspepsia			
subjects affected / exposed	16 / 249 (6.43%)	16 / 245 (6.53%)	
occurrences (all)	17	17	
Haemorrhoids			
subjects affected / exposed	18 / 249 (7.23%)	27 / 245 (11.02%)	
occurrences (all)	21	32	
Nausea			
subjects affected / exposed	137 / 249 (55.02%)	141 / 245 (57.55%)	
occurrences (all)	227	273	
Stomatitis			
subjects affected / exposed	36 / 249 (14.46%)	39 / 245 (15.92%)	
occurrences (all)	41	55	
Proctalgia			
subjects affected / exposed	5 / 249 (2.01%)	13 / 245 (5.31%)	
occurrences (all)	7	16	
Neutropenic colitis			
subjects affected / exposed	5 / 249 (2.01%)	13 / 245 (5.31%)	
occurrences (all)	5	14	
Vomiting			
subjects affected / exposed	63 / 249 (25.30%)	101 / 245 (41.22%)	
occurrences (all)	111	188	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 249 (5.62%)	11 / 245 (4.49%)	
occurrences (all)	14	11	
Dry skin			

subjects affected / exposed	8 / 249 (3.21%)	14 / 245 (5.71%)	
occurrences (all)	12	14	
Pruritus			
subjects affected / exposed	32 / 249 (12.85%)	28 / 245 (11.43%)	
occurrences (all)	37	33	
Petechiae			
subjects affected / exposed	21 / 249 (8.43%)	20 / 245 (8.16%)	
occurrences (all)	25	32	
Erythema			
subjects affected / exposed	20 / 249 (8.03%)	20 / 245 (8.16%)	
occurrences (all)	24	26	
Rash maculo-papular			
subjects affected / exposed	21 / 249 (8.43%)	17 / 245 (6.94%)	
occurrences (all)	23	24	
Rash			
subjects affected / exposed	87 / 249 (34.94%)	80 / 245 (32.65%)	
occurrences (all)	118	116	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	14 / 249 (5.62%)	22 / 245 (8.98%)	
occurrences (all)	18	25	
Pain in extremity			
subjects affected / exposed	15 / 249 (6.02%)	23 / 245 (9.39%)	
occurrences (all)	19	24	
Bone pain			
subjects affected / exposed	13 / 249 (5.22%)	7 / 245 (2.86%)	
occurrences (all)	14	8	
Back pain			
subjects affected / exposed	32 / 249 (12.85%)	26 / 245 (10.61%)	
occurrences (all)	42	29	
Infections and infestations			
Device related infection			
subjects affected / exposed	16 / 249 (6.43%)	9 / 245 (3.67%)	
occurrences (all)	18	9	
Sepsis			

subjects affected / exposed	13 / 249 (5.22%)	13 / 245 (5.31%)	
occurrences (all)	14	16	
Pneumonia			
subjects affected / exposed	29 / 249 (11.65%)	32 / 245 (13.06%)	
occurrences (all)	30	34	
Folliculitis			
subjects affected / exposed	4 / 249 (1.61%)	16 / 245 (6.53%)	
occurrences (all)	4	19	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	14 / 249 (5.62%)	11 / 245 (4.49%)	
occurrences (all)	17	12	
Decreased appetite			
subjects affected / exposed	40 / 249 (16.06%)	31 / 245 (12.65%)	
occurrences (all)	50	39	
Hypoalbuminaemia			
subjects affected / exposed	16 / 249 (6.43%)	18 / 245 (7.35%)	
occurrences (all)	16	19	
Hypocalcaemia			
subjects affected / exposed	24 / 249 (9.64%)	15 / 245 (6.12%)	
occurrences (all)	33	19	
Hypokalaemia			
subjects affected / exposed	102 / 249 (40.96%)	95 / 245 (38.78%)	
occurrences (all)	171	153	
Hypomagnesaemia			
subjects affected / exposed	20 / 249 (8.03%)	16 / 245 (6.53%)	
occurrences (all)	37	27	
Hypophosphataemia			
subjects affected / exposed	18 / 249 (7.23%)	16 / 245 (6.53%)	
occurrences (all)	23	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2018	No subject was enrolled into the study at the time of protocol amendment. Subjects who were screened in the CPKC412A2220 trial and confirmed to be FLT3 mutation negative (SR <0.05) could be offered the opportunity to participate in this study, CPKC412E2301, provided they met all the other inclusion criteria. This change was been made due to the implementation of Global Data Protection Regulation on 25-May-2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate.

Notes: