

**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	v2 (current)
This version publication date	14 July 2023
First version publication date	01 March 2022
Version creation reason	<ul style="list-style-type: none">• New data added to full data set Aligning the outcome measure (All Collected Deaths) and the Adverse Events time frame to the other Novartis published results on ClinicalTrials.gov & NovCTR database.

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	No
---------------------------------------	----

investigation plan (PIP)

Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? No

Notes:

Results analysis stage

Analysis stage Final

Date of interim/final analysis 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/m²/d, day 1 -3 (induction 1), 50 mg/m²/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/m²/d, days 1 -7 (induction 1), 1.5 g/m²/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/m²/d, day 1 -3 (induction 1), 10 mg/m²/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/m²/d, day 1 -3 (induction 1), 50 mg/m²/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/m²/d, days 1 -7 (induction 1), 1.5 g/m²/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/m²/d, day 1 -3 (induction 1), 10 mg/m²/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
Lack of efficacy	19	11
Guardian decision	1	1
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 count recovery 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 $\geq 1.0 \times 10^9/L$

platelets $\geq 100 \times 10^9/L$, 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 $\geq 1.0 \times 10^9/L$ and $50 \times 10^9/L \leq$ platelets $< 100 \times 10^9/L$

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 $\geq 0.5 \times 10^9/L$, Number of days from start of treatment to the first day neutrophils $\geq 1.0 \times 10^9/L$
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 $\geq 50 \times 10^9/L$ (partial platelet recovery), number of days from start of treatment to the first day platelets $\geq 100 \times 10^9/L$ (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.

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.

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.

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.

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 (\pm 37.8)	74.7 (\pm 72.3)	183 (\pm 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.

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 (\pm 101)	7.17 (\pm 57.8)	5.38 (\pm 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 II (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 (± 19.72)		

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.

Randomized but not treated deaths were collected after randomization but before treatment with study drug.

Post-treatment survival follow-up deaths 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	48	54		
Randomized but not treated deaths	2	1		
Deaths on-treatment (n = 245, 249)	25	21		
Post-treatment survival follow-up deaths	21	32		

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
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 occurrences (all)	21 / 249 (8.43%) 25	27 / 245 (11.02%) 46	
Oedema peripheral subjects affected / exposed occurrences (all)	38 / 249 (15.26%) 44	44 / 245 (17.96%) 54	
Chills subjects affected / exposed occurrences (all)	11 / 249 (4.42%) 13	16 / 245 (6.53%) 23	
Pain subjects affected / exposed occurrences (all)	8 / 249 (3.21%) 9	15 / 245 (6.12%) 17	
Pyrexia subjects affected / exposed occurrences (all)	138 / 249 (55.42%) 284	146 / 245 (59.59%) 308	
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	43 / 249 (17.27%) 57	44 / 245 (17.96%) 58	
Cough subjects affected / exposed occurrences (all)	37 / 249 (14.86%) 46	33 / 245 (13.47%) 37	
Dyspnoea subjects affected / exposed occurrences (all)	27 / 249 (10.84%) 35	28 / 245 (11.43%) 44	
Oropharyngeal pain subjects affected / exposed occurrences (all)	22 / 249 (8.84%) 25	17 / 245 (6.94%) 23	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	25 / 249 (10.04%) 29	16 / 245 (6.53%) 18	
Anxiety subjects affected / exposed occurrences (all)	15 / 249 (6.02%) 18	9 / 245 (3.67%) 12	
Investigations			

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

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

Abdominal pain upper subjects affected / exposed occurrences (all)	34 / 249 (13.65%) 40	24 / 245 (9.80%) 31	
Constipation subjects affected / exposed occurrences (all)	84 / 249 (33.73%) 118	77 / 245 (31.43%) 112	
Diarrhoea subjects affected / exposed occurrences (all)	142 / 249 (57.03%) 210	121 / 245 (49.39%) 185	
Dyspepsia subjects affected / exposed occurrences (all)	16 / 249 (6.43%) 17	16 / 245 (6.53%) 17	
Haemorrhoids subjects affected / exposed occurrences (all)	18 / 249 (7.23%) 21	27 / 245 (11.02%) 32	
Nausea subjects affected / exposed occurrences (all)	137 / 249 (55.02%) 227	141 / 245 (57.55%) 273	
Neutropenic colitis subjects affected / exposed occurrences (all)	5 / 249 (2.01%) 5	13 / 245 (5.31%) 14	
Vomiting subjects affected / exposed occurrences (all)	63 / 249 (25.30%) 111	101 / 245 (41.22%) 188	
Stomatitis subjects affected / exposed occurrences (all)	36 / 249 (14.46%) 41	39 / 245 (15.92%) 55	
Proctalgia subjects affected / exposed occurrences (all)	5 / 249 (2.01%) 7	13 / 245 (5.31%) 16	
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	32 / 249 (12.85%) 37	28 / 245 (11.43%) 33	
Alopecia			

subjects affected / exposed occurrences (all)	14 / 249 (5.62%) 14	11 / 245 (4.49%) 11	
Dry skin subjects affected / exposed occurrences (all)	8 / 249 (3.21%) 12	14 / 245 (5.71%) 14	
Erythema subjects affected / exposed occurrences (all)	20 / 249 (8.03%) 24	20 / 245 (8.16%) 26	
Petechiae subjects affected / exposed occurrences (all)	21 / 249 (8.43%) 25	20 / 245 (8.16%) 32	
Rash subjects affected / exposed occurrences (all)	87 / 249 (34.94%) 118	80 / 245 (32.65%) 116	
Rash maculo-papular subjects affected / exposed occurrences (all)	21 / 249 (8.43%) 23	17 / 245 (6.94%) 24	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	14 / 249 (5.62%) 18	22 / 245 (8.98%) 25	
Pain in extremity subjects affected / exposed occurrences (all)	15 / 249 (6.02%) 19	23 / 245 (9.39%) 24	
Bone pain subjects affected / exposed occurrences (all)	13 / 249 (5.22%) 14	7 / 245 (2.86%) 8	
Back pain subjects affected / exposed occurrences (all)	32 / 249 (12.85%) 42	26 / 245 (10.61%) 29	
Infections and infestations			
Device related infection subjects affected / exposed occurrences (all)	16 / 249 (6.43%) 18	9 / 245 (3.67%) 9	
Sepsis			

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