



## Clinical trial results:

### A Randomised, Open-label Study of Ponatinib Versus Nilotinib in Patients With Chronic Myeloid Leukemia in Chronic Phase Following Resistance to Imatinib

#### Summary

EudraCT number	2015-001318-92
Trial protocol	BE HU DE GB NL ES DK CZ PT FR AT PL
Global end of trial date	19 January 2021

#### Results information

Result version number	v1 (current)
This version publication date	13 November 2021
First version publication date	13 November 2021

#### Trial information

##### Trial identification

Sponsor protocol code	AP24534-15-303
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02627677
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2021
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the study was to demonstrate the efficacy of ponatinib administered at 2 starting doses (30 and 15 mg once daily [QD]) compared to nilotinib administered at 400 mg twice daily (BID) in participants with chronic phase-chronic myeloid leukemia (CP-CML) who are resistant to imatinib, as measured by major molecular response (MMR) by 12 months.

Protection of trial subjects:

All the participants were required to read and sign the informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 January 2016
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	Canada: 1
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 3
Country: Number of subjects enrolled	Russian Federation: 32
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Czechia: 2
Worldwide total number of subjects	44
EEA total number of subjects	8

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)	38
From 65 to 84 years	6
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 90 investigative sites in Austria, Canada, Czechia, France, Hungary, Italy, Korea, and Russia from 31 December 2015 to 20 January 2021

### Pre-assignment

Screening details:

Participants with a diagnosis of chronic phase-chronic myeloid leukemia were enrolled and randomised at a ratio of 1:2:1 to receive ponatinib 30 mg and ponatinib 15 mg compared with nilotinib 400 mg.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Cohort A: Ponatinib 30 mg

Arm description:

Ponatinib 30 mg, tablets, orally, once daily (QD) until achievement of major molecular response (MMR) up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 42 months.

Arm type	Experimental
Investigational medicinal product name	Ponatinib 30 mg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ponatinib 30 mg, taken orally once daily.

<b>Arm title</b>	Cohort B: Ponatinib 15 mg
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Arm description:

Ponatinib 15 mg, tablets, orally, QD until achievement of MMR up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 45 months.

Arm type	Experimental
Investigational medicinal product name	Ponatinib 15 mg QD
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ponatinib 15 mg, taken orally once daily.

<b>Arm title</b>	Cohort C: Nilotinib 400 mg
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Arm description:

Nilotinib 400 mg, tablets, orally, twice daily up to approximately 42 months.

Arm type	Active comparator
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Investigational medicinal product name	Nilotinib 400 mg BID
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nilotinib 400 mg, taken orally twice daily.

<b>Number of subjects in period 1</b>	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg
Started	11	21	12
Completed	0	0	0
Not completed	11	21	12
Physician decision	-	-	2
Adverse event (not progressive disease)	1	4	1
Pregnancy	-	1	-
Withdrawal by Subject	2	1	1
Study Terminated by Sponsor	5	10	6
Progressive disease	1	3	-
Lost to follow-up	-	-	1
Reason not Specified	-	-	1
Lack of efficacy	1	2	-
Randomised but not Treated	1	-	-

## Baseline characteristics

### Reporting groups

Reporting group title	Cohort A: Ponatinib 30 mg
Reporting group description: Ponatinib 30 mg, tablets, orally, once daily (QD) until achievement of major molecular response (MMR) up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 42 months.	
Reporting group title	Cohort B: Ponatinib 15 mg
Reporting group description: Ponatinib 15 mg, tablets, orally, QD until achievement of MMR up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 45 months.	
Reporting group title	Cohort C: Nilotinib 400 mg
Reporting group description: Nilotinib 400 mg, tablets, orally, twice daily up to approximately 42 months.	

Reporting group values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg
Number of subjects	11	21	12
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	43.7 ± 17.43	44.7 ± 15.53	54.3 ± 13.23
Gender categorical Units: Subjects			
Male	7	10	6
Female	3	11	6
Not recorded	1	0	0
Race (NIH/OMB) Units: Subjects			
Asian	2	4	1
White	7	16	10
Unknown or Not Reported	1	1	1
Not recorded	1	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	1
Not Hispanic or Latino	10	21	11
Not recorded	1	0	0
Height Units: cm			
Number analysed is the number of participants with data available for Height at Baseline. Height (n=10, 21, 11)			
arithmetic mean	172.9	169.4	168.8
standard deviation	± 9.62	± 9.35	± 9.17
Body Mass Index (BMI)			
BMI is calculated as weight (kg) divided by square of height (m <sup>2</sup> ). Number analysed is the number of			

participants with data available with BMI at Baseline. BMI (n=10, 21, 11)			
Units: kg/m <sup>2</sup>			
arithmetic mean	25.90	25.35	25.18
standard deviation	± 5.870	± 4.974	± 4.442
Weight			
Units: kg			
arithmetic mean	77.50	72.72	70.94
standard deviation	± 18.335	± 15.213	± 14.711

<b>Reporting group values</b>	Total		
Number of subjects	44		
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Male	23		
Female	20		
Not recorded	1		
Race (NIH/OMB)			
Units: Subjects			
Asian	7		
White	33		
Unknown or Not Reported	3		
Not recorded	1		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	42		
Not recorded	1		
Height			
Number analysed is the number of participants with data available for Height at Baseline. Height (n=10, 21, 11)			
Units: cm			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
BMI is calculated as weight (kg) divided by square of height (m <sup>2</sup> ). Number analysed is the number of participants with data available with BMI at Baseline. BMI (n=10, 21, 11)			
Units: kg/m <sup>2</sup>			
arithmetic mean			
standard deviation	-		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		

## End points

### End points reporting groups

Reporting group title	Cohort A: Ponatinib 30 mg
Reporting group description: Ponatinib 30 mg, tablets, orally, once daily (QD) until achievement of major molecular response (MMR) up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 42 months.	
Reporting group title	Cohort B: Ponatinib 15 mg
Reporting group description: Ponatinib 15 mg, tablets, orally, QD until achievement of MMR up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 45 months.	
Reporting group title	Cohort C: Nilotinib 400 mg
Reporting group description: Nilotinib 400 mg, tablets, orally, twice daily up to approximately 42 months.	
Subject analysis set title	Cohort A: Ponatinib 30 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Ponatinib 30 mg, tablets, orally, once daily (QD) until achievement of major molecular response (MMR) up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 42 months.	
Subject analysis set title	Cohort B: Ponatinib 15 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Ponatinib 15 mg, tablets, orally, QD until achievement of MMR up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 45 months.	
Subject analysis set title	Cohort C: Nilotinib 400 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Nilotinib 400 mg, tablets, orally, twice daily up to approximately 42 months.	

### Primary: Percentage of Participants with Major Molecular Response (MMR) Rate

End point title	Percentage of Participants with Major Molecular Response (MMR) Rate <sup>[1]</sup>
End point description: MMR is defined as the percentage of participants achieving a ratio of $\leq 0.1\%$ Breakpoint Cluster Region-Abelson (BCR ABL) to ABL transcripts on the international scale ( $\leq 0.1\%$ BCR-ABL/ABL[IS]) at any time within 12 months after randomisation. Safety Population included all participants who have received at least 1 dose of study drug, with data available for analysis.	
End point type	Primary
End point timeframe: Up to 12 months	

#### Notes:

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

Justification: Only descriptive statistics are reported for this outcome measure.



End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	11	
Units: percentage of participants				
number (confidence interval 95%)	40.0 (12.2 to 73.8)	33.3 (14.6 to 57.0)	45.5 (16.7 to 76.6)	

## Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants with Treatment Emergent Arterial Occlusive Events (TE-AOEs), Treatment Emergent Venous Thromboembolic Events (TE-VTE), Adverse Events (AEs), and Serious AEs (SAEs)

End point title	Percentage of Participants with Treatment Emergent Arterial Occlusive Events (TE-AOEs), Treatment Emergent Venous Thromboembolic Events (TE-VTE), Adverse Events (AEs), and Serious AEs (SAEs) <sup>[2]</sup>
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End point description:

TE-AOE: event with initial onset date on/after 1st dose date and no later than 30 days after last dose date of study treatment or events starting after initial consent that worsen in severity on/after 1st dose date. TE-VTE: vascular occlusive event with initial onset date on/after 1st dose date and no later than 30 days after last dose date of study treatment or events starting after initial consent that worsen in severity on/after 1st dose date. AE: any untoward medical occurrence in participant administered pharmaceutical product; untoward medical occurrence does not necessarily have causal relationship with this treatment. SAE: any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization/prolongation of existing hospitalization, results in persistent/incapacity, is congenital anomaly/birth defect/is medically important event. Safety Population: all participants who have received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

From first dose up to 30 days post last dose (Up to approximately 46 months)

Notes:

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

Justification: Only descriptive statistics are reported for this outcome measure.

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: percentage of participants				
number (not applicable)				
TE-AOE	0	4.8	8.3	
TE-VOEs	0	0	0	
AEs	100	95.2	100	
SAEs	40.0	14.3	16.7	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Major Cytogenetic Response (MCyR) Rates

End point title	Percentage of Participants with Major Cytogenetic Response (MCyR) Rates
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End point description:

MCyR was the percentage of participants achieving Complete cytogenetic response (CCyR: defined as 0% Philadelphia chromosome-positive [Ph+] metaphases by cytogenetic analysis of bone marrow) or Partial Cytogenetic Response (PCyR: defined as >0% to 35% Ph+ metaphases by cytogenetic analysis of bone marrow) at any time within 12 months after randomisation. Safety Population included all participants who have received at least 1 dose of study drug, with data available for analysis.

End point type	Secondary
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End point timeframe:

Up to 12 months

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	11	
Units: percentage of participants				
number (confidence interval 95%)	50.0 (18.7 to 81.3)	60.0 (36.1 to 80.9)	50.0 (21.1 to 78.9)	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with Complete Cytogenetic Response (CCyR) Rates

End point title	Percentage of Participants with Complete Cytogenetic Response (CCyR) Rates
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End point description:

CCyR rate was defined as the percentage of participants achieving CCyR up to 12 months after randomisation. CCyR is defined as 0% Philadelphia chromosome-positive [Ph+] metaphases by cytogenetic analysis of bone marrow. Safety Population included all participants who have received at least 1 dose of study drug, with data available for analysis.

End point type	Secondary
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End point timeframe:

Up to 12 months

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: percentage of participants				
number (confidence interval 95%)	40.0 (12.2 to 73.8)	55.0 (31.5 to 76.9)	50.0 (21.1 to 78.9)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Molecular Response (MR) Rate

End point title	Percentage of Participants with Molecular Response (MR) Rate
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End point description:

Molecular response rate is defined as percentage of participants achieving MR2: Molecular response with 2-log reduction (defined as  $\leq 1\%$  BCR-ABL[IS]), MMR: Major molecular responder, MR4 (defined as  $\leq 0.01\%$  BCR-ABL[IS]), and MR4.5 (defined as  $\leq 0.0032\%$  BCR-ABL[IS]) after randomisation. Safety Population included all participants who have received at least 1 dose of study drug, with data available for analysis.

End point type	Secondary
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End point timeframe:

From Month 3 to every 3 months up to 48 months

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	11	
Units: percentage of participants				
number (not applicable)				
MR2 - Month 3	70.0	38.1	45.5	
MR2 - Month 6	60.0	57.1	54.5	
MR2 - Month 9	50.0	52.4	45.5	
MR2 - Month 12	50.0	52.4	54.5	
MR2 - Month 15	50.0	52.4	54.5	
MR2 - Month 18	50.0	47.6	54.5	
MR2 - Month 21	50.0	52.4	45.5	
MR2 - Month 24	50.0	47.6	54.5	
MR2 - Month 27	50.0	42.9	54.5	
MR2 - Month 30	50.0	38.1	45.5	
MR2 - Month 33	30.0	33.3	27.3	
MR2 - Month 36	50.0	33.3	36.4	
MR2 - Month 39	20.0	14.3	18.2	
MR2 - Month 42	10.0	9.5	9.1	
MR2 - Month 45	10.0	14.3	9.1	
MR2 - Month 48	10.0	4.8	9.1	
MR3/MMR - Month 3	30.0	4.8	18.2	

MR3/MMR - Month 6	30.0	28.6	36.4	
MR3/MMR - Month 9	30.0	28.6	45.5	
MR3/MMR - Month 12	40.0	33.3	45.5	
MR3/MMR - Month 15	40.0	28.6	45.5	
MR3/MMR - Month 18	40.0	38.1	45.5	
MR3/MMR - Month 21	40.0	33.3	45.5	
MR3/MMR - Month 24	40.0	33.3	45.5	
MR3/MMR - Month 27	40.0	33.3	45.5	
MR3/MMR - Month 30	40.0	33.3	45.5	
MR3/MMR - Month 33	20.0	28.6	27.3	
MR3/MMR - Month 36	40.0	28.6	36.4	
MR3/MMR - Month 39	20.0	14.3	18.2	
MR3/MMR - Month 42	10.0	9.5	9.1	
MR3/MMR - Month 45	10.0	9.5	9.1	
MR3/MMR - Month 48	10.0	4.8	9.1	
MR4 - Month 3	0.0	0.0	0.0	
MR4 - Month 6	20.0	14.3	9.1	
MR4 - Month 9	10.0	9.5	18.2	
MR4 - Month 12	10.0	9.5	27.3	
MR4 - Month 15	10.0	19.0	27.3	
MR4 - Month 18	20.0	23.8	27.3	
MR4 - Month 21	20.0	9.5	36.4	
MR4 - Month 24	10.0	19.0	36.4	
MR4 - Month 27	20.0	19.0	36.4	
MR4 - Month 30	20.0	14.3	36.4	
MR4 - Month 33	0.0	14.3	9.1	
MR4 - Month 36	10.0	19.0	27.3	
MR4 - Month 39	20.0	4.8	18.2	
MR4 - Month 42	10.0	0.0	9.1	
MR4 - Month 45	10.0	4.8	9.1	
MR4 - Month 48	10.0	0.0	9.1	
MR4.5 - Month 3	0.0	0.0	0.0	
MR4.5 - Month 6	20.0	0.0	0.0	
MR4.5 - Month 9	0.0	4.8	9.1	
MR4.5 - Month 12	0.0	4.8	18.2	
MR4.5 - Month 15	10.0	4.8	9.1	
MR4.5 - Month 18	10.0	9.5	9.1	
MR4.5 - Month 21	10.0	9.5	27.3	
MR4.5 - Month 24	10.0	4.8	18.2	
MR4.5 - Month 27	10.0	14.3	18.2	
MR4.5 - Month 30	10.0	4.8	27.3	
MR4.5 - Month 33	0.0	4.8	0.0	
MR4.5 - Month 36	10.0	9.5	18.2	
MR4.5 - Month 39	10.0	4.8	18.2	
MR4.5 - Month 42	10.0	0.0	9.1	
MR4.5 - Month 45	10.0	0.0	9.1	
MR4.5 - Month 48	0.0	0.0	9.1	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants with MR1

End point title	Percentage of Participants with MR1
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End point description:

MR1 was defined as the percentage of participants achieving a ratio of  $\leq 10\%$  BCR ABL to ABL transcripts on the international scale at 3 months. Safety Population includes all participants who have received at least 1 dose of study drug, with data available for analysis.

End point type	Secondary
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End point timeframe:

Month 3

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	11	
Units: percentage of participants				
number (not applicable)	70.0	66.7	63.6	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Response

End point title	Time to Response
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End point description:

Time to MMR defined as the interval between the randomisation date and the first date at which the criteria for response was met. MMR was defined as  $\leq 0.1\%$  BCR-ABL. Safety Population includes all participants who have received at least 1 dose of study drug. Only responders were analyzed for this outcome measure. 99999 indicates that the upper limit of confidence interval (CI) was not estimable due to less number of participants with event.

End point type	Secondary
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End point timeframe:

Up to 12 months

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	9	5	
Units: months				
median (confidence interval 95%)	3.07 (3.0 to 99999)	6.29 (3.0 to 18.1)	6.07 (3.0 to 99999)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of response

End point title	Duration of response
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End point description:

Duration of response defined as the interval between the first assessment at which the criteria for response was met until the earliest date at which loss of response occurs, or the criteria for progression was met. Safety Population includes all participants who have received at least 1 dose of study drug. 99999 indicates that the median, lower limit and upper limit of CI were not estimable due to less number of participants with event.

End point type	Secondary
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End point timeframe:

Up to approximately 60 months

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (3.0 to 99999)	99999 (99999 to 99999)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
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End point description:

Progression-free survival (PFS) defined as the interval between the first dose date of study treatment and the first date at which the criteria for progression was met (progression to AP- or BP CML), or death due to any cause, censored at the last response assessment. Safety Population includes all participants who have received at least 1 dose of study drug. 99999 indicates that the median, lower limit and upper limit of CI were not estimable due to less number of participants with event.

End point type	Secondary
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End point timeframe:

Up to end of study (approximately 60 months)

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: months				
median (confidence interval 95%)	99999 (8.0 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival (OS) defined as the interval between the first dose date of study treatment and date of death due to any cause, censored at the last contact date to be alive. Safety Population includes all participants who have received at least 1 dose of study drug. 99999 indicates that the median, lower limit and upper limit of CI were not estimable due to less number of participants with event.	
End point type	Secondary
End point timeframe:	
Up to end of study (approximately 60 months)	

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: months				
median (confidence interval 95%)	99999 (18.5 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants who Achieved/Maintained Complete Hematologic Response (CHR)

End point title	Percentage of Participants who Achieved/Maintained Complete Hematologic Response (CHR)
End point description:	
CHR rate is defined as the percentage of participants achieving CHR at any time after initiation of study	

treatment. CHR is defined as achieving all of the following measurements: White blood cells (WBC)  $\leq$  institutional upper limit of normal (ULN); Platelets  $<450 \times 10^9/L$ ; No blasts or promyelocytes in peripheral blood;  $<5\%$  myelocytes plus metamyelocytes in peripheral blood; Basophils in peripheral blood  $<5\%$ ; No extramedullary involvement (including no hepatomegaly or splenomegaly). Safety Population includes all participants who have received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

3 months after the first dose of study treatment

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: percentage of participants				
median (confidence interval 95%)	60.0 (26.2 to 87.8)	81.0 (58.1 to 94.6)	50.0 (21.1 to 78.9)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Treatment Emergent AEs Leading to Treatment Discontinuation, Dose Reduction and Dose Interruption

End point title	Percentage of Participants with Treatment Emergent AEs Leading to Treatment Discontinuation, Dose Reduction and Dose Interruption
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End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. Safety Population includes all participants who have received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From first dose up to end of treatment (Up to approximately 45 months)

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	21	12	
Units: percentage of participants				
number (not applicable)				
TEAEs Leading to Treatment Discontinuation	10.0	23.8	25.0	
TEAEs Leading to Dose Reduction	40.0	19.0	33.3	
TEAEs Leading to Dose Interruption	70.0	38.1	41.7	



## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Progression to Accelerated Phase (AP) or Blast Phase (BP)-CML

End point title	Percentage of Participants with Progression to Accelerated Phase (AP) or Blast Phase (BP)-CML
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End point description:

Progression to AP is defined as:  $\geq 15\%$  and  $< 30\%$  blasts in peripheral blood or bone marrow or  $\geq 20\%$  basophils in peripheral blood or bone marrow or  $\geq 30\%$  blasts + promyelocytes in peripheral blood or bone marrow (but  $< 30\%$  blasts) or  $< 100 \times 10^9$  platelets/L in peripheral blood unrelated to therapy or cytogenetic, genetic evidence of clonal evolution, and no extramedullary disease. Progression to BP-CML is defined as:  $\geq 30\%$  blasts in peripheral blood or bone marrow or extramedullary disease other than hepatosplenomegaly.

End point type	Secondary
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End point timeframe:

Up to end of study (Up to approximately 60 months)

End point values	Cohort A: Ponatinib 30 mg	Cohort B: Ponatinib 15 mg	Cohort C: Nilotinib 400 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 <sup>[3]</sup>	0 <sup>[4]</sup>	0 <sup>[5]</sup>	
Units: participants				

Notes:

[3] - As the study was terminated, data was not collected and analyzed for this outcome measure.

[4] - As the study was terminated, data was not collected and analyzed for this outcome measure.

[5] - As the study was terminated, data was not collected and analyzed for this outcome measure.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From first dose up to end of study (Up to approximately 60 months); for serious and other adverse events: from first dose up to 30 days post last dose (Up to approximately 46 months)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment. Safety Population includes participants who have received at least 1 dose of study drug.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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### Reporting groups

Reporting group title	Cohort A: Ponatinib 30 mg
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Reporting group description:

Ponatinib 30 mg, tablets, orally, once daily (QD) until achievement of major molecular response (MMR) up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 42 months.

Reporting group title	Cohort C: Nilotinib 400 mg
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Reporting group description:

Nilotinib 400 mg, tablets, orally, twice daily up to approximately 42 months.

Reporting group title	Cohort B: Ponatinib 15 mg
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Reporting group description:

Ponatinib 15 mg, tablets, orally, QD until achievement of MMR up to 12 months. Once MMR was achieved, participants received reduced dose of ponatinib 15 mg orally once daily up to approximately 45 months.

Serious adverse events	Cohort A: Ponatinib 30 mg	Cohort C: Nilotinib 400 mg	Cohort B: Ponatinib 15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	2 / 12 (16.67%)	3 / 21 (14.29%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
Investigations			
Platelet count decreased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			

subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Musculoskeletal and connective tissue disorders</b>			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Infections and infestations</b>			
Pneumonia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1

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

<b>Non-serious adverse events</b>	Cohort A: Ponatinib 30 mg	Cohort C: Nilotinib 400 mg	Cohort B: Ponatinib 15 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	12 / 12 (100.00%)	20 / 21 (95.24%)
<b>Vascular disorders</b>			
Essential hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	2 / 21 (9.52%)
occurrences (all)	4	1	8

Peripheral artery stenosis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
General disorders and administration site conditions			
Pyrexia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	3 / 12 (25.00%) 4	1 / 21 (4.76%) 1
Asthenia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Bronchial obstruction subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Pulmonary artery dilatation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Pulmonary hypertension subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Throat irritation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 14	2 / 12 (16.67%) 2	1 / 21 (4.76%) 4
Blood cholesterol increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	3 / 12 (25.00%) 4	2 / 21 (9.52%) 2
Platelet count decreased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 12	0 / 12 (0.00%) 0	2 / 21 (9.52%) 7
Lipase increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 12 (16.67%) 4	1 / 21 (4.76%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 10	2 / 12 (16.67%) 2	0 / 21 (0.00%) 0
Platelet count increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Weight increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3	0 / 12 (0.00%) 0	1 / 21 (4.76%) 1
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 12 (8.33%) 4	0 / 21 (0.00%) 0
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Blood magnesium decreased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Blood triglycerides increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	5	0	0
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Procedural pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Paternal exposure timing unspecified			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Thermal burn			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Cardiac disorders			
Left ventricular hypertrophy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	0 / 12 (0.00%) 0	2 / 21 (9.52%) 2
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Sinus arrhythmia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 12 (0.00%) 0	0 / 21 (0.00%) 0
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Dilatation atrial subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Right atrial hypertrophy subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Right ventricular dilatation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 12 (8.33%) 1	0 / 21 (0.00%) 0



Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	5 / 10 (50.00%)	2 / 12 (16.67%)	5 / 21 (23.81%)
occurrences (all)	24	13	27
Anaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 12 (0.00%)	3 / 21 (14.29%)
occurrences (all)	11	0	4
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 12 (16.67%)	3 / 21 (14.29%)
occurrences (all)	10	15	7
Anaemia folate deficiency			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Thrombocytosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 21 (4.76%)
occurrences (all)	0	1	2
Splenic lesion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Retinal vascular disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Periorbital oedema			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	2 / 21 (9.52%)
occurrences (all)	0	1	2
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dental caries			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Pancreatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Inguinal hernia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Ocular icterus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 12 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Dermatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Rash papular			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	4 / 21 (19.05%)
occurrences (all)	1	2	5
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	4 / 21 (19.05%)
occurrences (all)	0	3	4
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	1 / 12 (8.33%)	3 / 21 (14.29%)
occurrences (all)	2	1	4
Musculoskeletal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Spinal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hepatitis viral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	2
Diabetes mellitus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hyperlipidaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hypercholesterolaemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 12 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			

subjects affected / exposed	1 / 10 (10.00%)	0 / 12 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 12 (8.33%)	1 / 21 (4.76%)
occurrences (all)	0	1	1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2016	Amendment 2: Imposed more stringent and detailed guidelines for contraception requirements of participants on the study. Excluded participants with hypersensitivity to the ponatinib or nilotinib active substances or to any of their inactive ingredients. Added Hepatitis B virus serology as a screening requirement. Increased the blood count and lipase monitoring frequency (additional screens on Day 15 during Cycle 2 and Cycle 3) in adherence to the ponatinib Investigator's Brochure. Changed statistical testing scheme to use Bonferroni procedure rather than Hochberg procedure to adjust for comparisons of Cohorts A and B to Cohort C. Updated the Schedule of Events to allow another option (brain natriuretic peptide testing) for sites unable to perform N-terminal pro-brain natriuretic peptide testing. Added requirements for an eye exam at screening and throughout treatment period as clinically indicated. Provided guidance for ocular toxicity. Corrected dose modification for nilotinib for Grade 3 peripheral vascular arterial events, QT interval corrected (Fridericia) (QTcF) prolongation and amylase/lipase elevations. Updated sponsor contact information.

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.

This study was terminated due to operational feasibility and not due to any safety concerns.

Notes: