Clinical trial results:
A Pivotal Phase 1/2, Single-Arm, Open-label Study to Evaluate the Safety and Efficacy of Ponatinib With Chemotherapy in Pediatric Patients With Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Who Have Relapsed or Are Resistant or Intolerant to a Prior Tyrosine Kinase Inhibitor-Containing Therapy, or Who Have the T315I Mutation

Summary

EudraCT number	2019-002549-39
Trial protocol	GB FR CZ NL IT PL PT ES
Global end of trial date	19 July 2024

Results information

Result version number	v1 (current)
This version publication date	04 January 2025
First version publication date	04 January 2025

Trial information

Trial identification

Sponsor protocol code	Ponatinib-1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04501614
WHO universal trial number (UTN)	U1111-1225-0394

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, Massachusetts, United States, 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001186-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to determine the recommended phase 2 dose (RP2D) and rate of complete remission (CR) at the end of the reinduction block of ponatinib (tablet and age-appropriate formulation [AAF]) in combination with chemotherapy.

Protection of trial subjects:

Each participant or their guardians were required to sign an informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2021
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	China: 5
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Brazil: 1
Worldwide total number of subjects	11
EEA total number of subjects	3

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)	4
Adolescents (12-17 years)	6

Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with a diagnosis of Philadelphia Chromosome-Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) took part in the study at various investigative sites globally from 24 February 2021 to 19 July 2024.

Pre-assignment

Screening details:

Participants were enrolled in Phase 1 & received ponatinib per protocol. Due to multiple dose-limiting toxicities(DLTs) in Phase 1,enrollment was terminated & no recommended phase 2 dose(RP2D) was determined. Sponsor terminated study after 6-month follow-up & no participants were enrolled in Phase 2 of study. Thus, no Phase 2 results are presented.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ponatinib 30 mg Adult Equivalent

Arm description:

Participants received weight-based dose of ponatinib tablets 30 milligrams (mg) adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.

Arm type	Experimental
Investigational medicinal product name	Ponatinib
Investigational medicinal product code	
Other name	Ponatinib AAF, Chemotherapy Agents
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received weight-based doses of ponatinib tablets equivalent to 30 mg in adults, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment followed by rest period from chemotherapy for a minimum of 6 days consisting of daily ponatinib only) up to Week 8 in Phase 1.

Arm title	Ponatinib 15 mg Adult Equivalent

Arm description:

Participants received weight-based dose of ponatinib tablets 15 mg adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.

Arm type	Experimental
Investigational medicinal product name	Ponatinib
Investigational medicinal product code	
Other name	Ponatinib AAF, Chemotherapy agents
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received weight-based doses of ponatinib tablets equivalent to 15 mg in adults, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment followed by rest period from chemotherapy for a minimum of 6 days consisting of daily ponatinib only) up to Week 8 in Phase 1.

Number of subjects in period 1	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent
Started	7	4
Completed	0	0
Not completed	7	4
Withdrawal by Participant (Parent/Legal Guardian)	1	1
Study Terminated by Sponsor	6	3

Baseline characteristics

Reporting groups	
Reporting group title	Ponatinib 30 mg Adult Equivalent
Reporting group description:	
Participants received weight-based dose of ponatinib tablets 30 milligrams (mg) adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.	
Reporting group title	Ponatinib 15 mg Adult Equivalent
Reporting group description:	
Participants received weight-based dose of ponatinib tablets 15 mg adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.	

Reporting group values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent	Total
Number of subjects	7	4	11
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	12.1	13.5	
standard deviation	± 2.41	± 3.70	-
Gender categorical Units: Subjects			
Female	4	2	6
Male	3	2	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	2	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	6	3	9
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Ponatinib 30 mg Adult Equivalent

Reporting group description:

Participants received weight-based dose of ponatinib tablets 30 milligrams (mg) adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.

Reporting group title	Ponatinib 15 mg Adult Equivalent

Reporting group description:

Participants received weight-based dose of ponatinib tablets 15 mg adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.

Subject analysis set title	Ponatinib RP2D
Subject analysis set type	Per protocol

Subject analysis set description:

Participants were planned to receive weight-based dose of ponatinib tablets at the RP2D adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator's discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) followed by optional ponatinib continuation with or without chemotherapy in Phase 2.

Primary: Phase 2: Percentage of Participants with Complete Remission (CR) at the End of the Reinduction Block

End point title	Phase 2: Percentage of Participants with Complete Remission (CR) at the End of the Reinduction Block[1]

End point description:

CR was defined as no circulating blasts and less than (<)5 percent (%) blasts in the bone marrow (BM); normal maturation of all cellular components in the bone marrow; no extramedullary disease; absolute neutrophil count (ANC) greater than (>)1000 cells/microliter (µL) (or >1.0 × 10^9 cells/liter [L]); Platelets >100,000/µL (or >100 × 10^9 platelets/L). The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Primary

End point timeframe:

Up to Day 35 in Phase 2

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: No data was collected as no participants were enrolled in Phase 2.

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[2]			
Units: percentage of participants				
number (not applicable)				

Notes:

[2] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1: Recommended Phase 2 Dose (RP2D) of Ponatinib in Combination With Chemotherapy

End point title	Phase 1: Recommended Phase 2 Dose (RP2D) of Ponatinib in Combination With Chemotherapy[3]

End point description:

The RP2D is the maximum tolerated dose (MTD) or less. '99999' indicates that due to DLTs observed in both dose cohorts, study enrollment was terminated per protocol and participants were discontinued from study treatment per independent data monitoring committee (IDMC) advice followed by study termination by Sponsor. Thus, the RP2D could not be determined. The Safety Population included all participants who received at least 1 dose of ponatinib.

End point type	Primary

End point timeframe:

Up to Day 35 in Phase 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to DLTs observed in both dose cohorts, study enrollment was terminated per protocol and participants were discontinued from study treatment per independent data monitoring committee (IDMC) advice followed by study termination by Sponsor. Thus, the RP2D could not be determined.

End point values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: milligrams per square meter (mg/m^2)				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Number of Participants with CR at the end of Reinduction Block

End point title	Phase 1: Number of Participants with CR at the end of Reinduction Block

End point description:

CR was defined as no circulating blasts and <5% blasts in the BM; normal maturation of all cellular components in the bone marrow; no extramedullary disease; ANC >1000 cells/µL (or >1.0 × 10^9 cells/L); Platelets >100,000/µL (or >100 × 10^9 platelets/L). The Safety Population included all participants who received at least 1 dose of ponatinib. Overall number of participants analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Day 35 in Phase 1

End point values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Ph+ ALL Participants who Achieved CR at the End of Consolidation Block

End point title	Phase 2: Percentage of Ph+ ALL Participants who Achieved CR at the End of Consolidation Block

End point description:

CR was defined as no circulating blasts and <5% blasts in the bone marrow; normal maturation of all cellular components in the bone marrow; no extramedullary disease; ANC >1000 cells/µL (or >1.0 × 10^9 cells/L); Platelets >100,000 platelets/µL (or >100 × 10^9 platelets/L). The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Day 70 in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[4]			
Units: percentage of participants				
number (not applicable)				

Notes:

[4] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Event-free Survival (EFS)

End point title	Phase 2: Event-free Survival (EFS)

End point description:

EFS was defined as time from date of enrollment until death due to any cause; refractory to treatment (defined as failure to achieve CR by end of the consolidation block) or relapse from CR. CR was defined as no circulating blasts and <5% blasts in the bone marrow; normal maturation of all cellular components in the bone marrow; no extramedullary disease; ANC >1000 cells/µL (or >1.0 × 10^9 cells/L); Platelets >100,000 platelets/µL (or >100 × 10^9 platelets/L). The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to 3 years of follow-up in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[5]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[5] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Ph+ ALL Participants with Negative Minimal Residual Disease (MRD) Among Those who Achieved CR

End point title	Phase 2: Percentage of Ph+ ALL Participants with Negative Minimal Residual Disease (MRD) Among Those who Achieved CR

End point description:

MRD negative rate is the percentage of participants who achieve MRD negative status by evaluation of bone marrow aspirate at <0.01% threshold. The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to Day 70 (end of consolidation block) in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[6]			
Units: participants				

Notes:

[6] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants who Relapsed or Progressed Following Reinduction and Consolidation

End point title	Phase 2: Percentage of Participants who Relapsed or Progressed Following Reinduction and Consolidation

End point description:

The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1

and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to 3 years of follow-up in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[7]			
Units: participants				

Notes:

[7] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Percentage of Participants Who Underwent Hematopoietic Stem Cell Transplantation (HSCT)

End point title	Phase 2: Percentage of Participants Who Underwent Hematopoietic Stem Cell Transplantation (HSCT)

End point description:

The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to 3 years of follow-up in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[8]			
Units: participants				

Notes:

[8] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)

End point description:

OS was defined as time from first dose of ponatinib until death due to any cause. The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No

data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to 3 years of follow-up in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[9]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[9] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DOR)

End point title	Phase 2: Duration of Response (DOR)

End point description:

DOR was defined as the interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs. CR was defined as no circulating blasts and <5% blasts in the bone marrow; normal maturation of all cellular components in the bone marrow; no extramedullary disease; ANC >1000 cells/µL (or >1.0 × 10^9 cells/L); Platelets >100,000 platelets/µL (or >100 × 10^9 platelets /L). The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to 3 years of follow-up in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[10]			
Units: participants				

Notes:

[10] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival (PFS)

End point title	Phase 2: Progression-free Survival (PFS)

End point description:

PFS was defined as time from date of enrolment until death related to disease under study; disease progression (clinical deterioration associated with disease process, including evidence of increasing blasts in the bone marrow from baseline and/or evidence of new organ involvement) or relapse from CR. CR was defined as no circulating blasts and <5% blasts in the bone marrow; normal maturation of all cellular components in the bone marrow; no extramedullary disease; ANC >1000 cells/µL (or >1.0 × 10^9 cells/L); Platelets >100,000 platelets/µL (or >100 × 10^9 platelets/L). The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated. No data was collected as no participants were enrolled in Phase 2.

End point type	Secondary

End point timeframe:

Up to 3 years of follow-up in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[11]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[11] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: AUClast: Area Under the Plasma Concentration-Time Curve From Time 0 to the Time of the Last Quantifiable Concentration for Ponatinib

End point title	Phase 1: AUClast: Area Under the Plasma Concentration-Time Curve From Time 0 to the Time of the Last Quantifiable Concentration for Ponatinib

End point description:

'99999' indicates geometric CV was not estimable for a single participant. The PK Analysis Population included all participants in the Phase 1 portion of the study who had sufficient ponatinib dosing data and concentration-time data to permit the calculation of ponatinib PK parameters. Number analyzed is the number of participants with data available for analysis for the specified timepoint.

End point type	Secondary

End point timeframe:

Predose and at multiple timepoints post-dose up to 24 hours on Days 1 and 22 in Phase 1

End point values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: h*ng/ml				
geometric mean (geometric coefficient of variation)				
Day 1	883 (± 22.8)	264 (± 62.1)		

Day 22	2800 (± 99999)	815 (± 83.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Tmax: Time of First Occurrence of Cmax for Ponatinib

End point title	Phase 1: Tmax: Time of First Occurrence of Cmax for Ponatinib

End point description:

'99999' indicates full range was not estimable for a single participant. The PK Analysis Population included all participants in the Phase 1 portion of the study who had sufficient ponatinib dosing data and concentration-time data to permit the calculation of ponatinib PK parameters. Number analyzed is the number of participants with data available for analysis for the specified timepoint.

End point type	Secondary

End point timeframe:

Predose and at multiple timepoints post-dose up to 24 hours on Days 1 and 22 in Phase 1

End point values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: hours				
median (full range (min-max))				
Day 1	6.00 (2.0 to 7.5)	3.99 (3.8 to 4.1)		
Day 22	4.08 (-99999 to 99999)	3.92 (2.0 to 5.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Cmax: Maximum Observed Plasma Concentration for Ponatinib

End point title	Phase 1: Cmax: Maximum Observed Plasma Concentration for Ponatinib

End point description:

'99999' indicates geometric coefficient of variation (CV) was not estimable for a single participant. The Pharmacokinetic (PK) Analysis Population included all participants in the Phase 1 portion of the study who had sufficient ponatinib dosing data and concentration-time data to permit the calculation of ponatinib PK parameters. Number analyzed is the number of participants with data available for analysis for the specified timepoint.

End point type	Secondary

End point timeframe:

Predose and at multiple timepoints post-dose up to 24 hours on Days 1 and 22 in Phase 1

End point values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: nanograms/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1	65.8 (± 29.5)	24.9 (± 71.1)		
Day 22	183 (± 99999)	47.7 (± 92.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1: Number of Participants with Treatment-emergent Adverse Events (TEAEs), Serious TEAEs, Venous Thrombotic/Embolic Events (VTEs), and Adverse Events of Special Interest (AESIs)

End point title	Phase 1: Number of Participants with Treatment-emergent Adverse Events (TEAEs), Serious TEAEs, Venous Thrombotic/Embolic Events (VTEs), and Adverse Events of Special Interest (AESIs)

End point description:

AE: any untoward medical occurrence in clinical study participant,temporally associated with use of study intervention,whether/not occurrence was considered related to study intervention including any unfavorable & unintended sign (eg,clinically significant abnormal laboratory finding),symptom/disease.TEAE: any AE that occurs after administration of first dose of any study drug & through 30 days after last dose of any study drug.Serious TEAE:AE that at any dose resulted in death,was life-threatening,required inpatient hospitalisation/prolongation of existing hospitalisation,resulted in persistent/significant incapacity,was congenital anomaly/birth defect,was medically important event. AESI: Protocol-defined AEs resulting in compromise of organ function/other significant consequences. VTEs were identified as AESIs for ponatinib & included arterial, VTEs that meet criteria for serious TEAEs. The Safety Population included all participants who received at least 1 dose of

End point type	Secondary

End point timeframe:

Up to 34.8 months in Phase 1

End point values	Ponatinib 30 mg Adult Equivalent	Ponatinib 15 mg Adult Equivalent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: participants				
TEAEs	7	4		
Serious TEAEs	5	2		
VTEs	0	0		
AESIs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants With TEAEs, Serious TEAEs, VTEs, and AESIs

End point title	Phase 2: Number of Participants With TEAEs, Serious TEAEs, VTEs, and AESIs

End point description:

AE:untoward medical occurrence in study participant,temporally associated with use of intervention,whether/not occurrence was considered related to intervention including any unfavorable&unintended sign(eg,clinically significant abnormal laboratory finding),symptom/disease.TEAE:AE that occurs after administration of first dose of any study drug & through 30 days after last dose of any study drug.Serious TEAE:AE that at any dose resulted in death,was life-threatening,required inpatient hospitalisation/prolongation of existing hospitalisation,resulted in persistent/significant incapacity,was congenital anomaly/birth defect,was medically important event.AESI:Protocol-defined AEs resulting in compromise of organ function/other significant consequences.VTEs were identified as AESIs for ponatinib & included arterial,VTEs that meet criteria for serious TEAEs.Study enrollment was terminated per protocol due to DLTs in Phase 1. No data

End point type	Secondary

End point timeframe:

Up to 30 days after last dose of ponatinib in Phase 2

End point values	Ponatinib RP2D			
Subject group type	Subject analysis set			
Number of subjects analysed	0[12]			
Units: participants				

Notes:

[12] - No data was collected as no participants were enrolled in Phase 2 due to study termination.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 34.8 months in Phase 1

Adverse event reporting additional description:

The Safety Population included all participants who received at least 1 dose of ponatinib. The study was terminated following the Sponsor's decision attributed to DLTs observed in Phase 1. Hence, no participants were enrolled in Phase 2 of the study and no data for the same could be presented.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Ponatinib 15 mg Adult Equivalent

Reporting group description:

Participants received weight-based dose of ponatinib tablets 15 mg adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator’s discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.

Reporting group title	Ponatinib 30 mg Adult Equivalent

Reporting group description:

Participants received weight-based dose of ponatinib tablets 30 mg adult-equivalent, orally, once daily in combination with chemotherapy backbone per standard regimen at the investigator’s discretion in both reinduction block and consolidation block (35 days each including 29 days of treatment in combination with chemotherapy followed by a minimum 6-day rest period from chemotherapy with daily ponatinib only) up to Day 70 (end of consolidation) followed by optional ponatinib continuation in Phase 1.

Serious adverse events	Ponatinib 15 mg Adult Equivalent	Ponatinib 30 mg Adult Equivalent	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	5 / 7 (71.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilirubin conjugated increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (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			

Cerebral haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ventricle dilatation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
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			
Catheter site haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Disseminated mucormycosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ponatinib 15 mg Adult Equivalent	Ponatinib 30 mg Adult Equivalent	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	7 / 7 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	5	
Deep vein thrombosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Chest discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Facial pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	1	3	
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	7	
Swelling			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Anxiety			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 4 (25.00%)	4 / 7 (57.14%)	
occurrences (all)	5	15	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	4	5	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 4 (100.00%)	7 / 7 (100.00%)	
occurrences (all)	20	56	
Amylase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Antithrombin III decreased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	15	
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 4 (75.00%)	7 / 7 (100.00%)	
occurrences (all)	16	33	
Bilirubin conjugated increased			
subjects affected / exposed	2 / 4 (50.00%)	1 / 7 (14.29%)	
occurrences (all)	10	1	
Blood albumin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	6	
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	7	
Blood calcium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood fibrinogen decreased			
subjects affected / exposed	1 / 4 (25.00%)	4 / 7 (57.14%)	
occurrences (all)	2	12	
Blood glucose increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	6	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	4	
Blood magnesium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Blood phosphorus decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	4	
Blood triglycerides increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	6		
C-reactive protein increased				
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Electrocardiogram QT prolonged				
subjects affected / exposed	3 / 4 (75.00%)	0 / 7 (0.00%)		
occurrences (all)	4	0		
Electrocardiogram T wave abnormal				
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Eosinophil count decreased				
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Gamma-glutamyltransferase increased				
subjects affected / exposed	3 / 4 (75.00%)	6 / 7 (85.71%)		
occurrences (all)	14	20		
Glycosylated haemoglobin increased				
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Lipase increased				
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Lymphocyte count decreased				
subjects affected / exposed	2 / 4 (50.00%)	4 / 7 (57.14%)		
occurrences (all)	8	62		
Monocyte count increased				
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Neutrophil count decreased				
subjects affected / exposed	3 / 4 (75.00%)	5 / 7 (71.43%)		
occurrences (all)	11	40		
Neutrophil count increased				
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	2		

Platelet count decreased			
subjects affected / exposed	3 / 4 (75.00%)	4 / 7 (57.14%)	
occurrences (all)	10	38	
Platelet count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Protein total decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Protein urine present			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
White blood cell count decreased			
subjects affected / exposed	3 / 4 (75.00%)	4 / 7 (57.14%)	
occurrences (all)	23	48	
Prothrombin time prolonged			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
White blood cells urine positive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	5	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Lip injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Mouth injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vascular injury			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Ventricular hypertrophy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cerebral haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Mental impairment			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hemiplegia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hemiparesis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	1 / 4 (25.00%)	5 / 7 (71.43%)	
occurrences (all)	1	8	
Neuropathy peripheral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 4 (100.00%)	7 / 7 (100.00%)	
occurrences (all)	30	51	
Coagulopathy			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Leukopenia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	6	13	
Hypofibrinogenaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	8	0	
Hypercoagulation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	14	

Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 7 (42.86%)	
occurrences (all)	23	16	
Neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	17	
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	2 / 4 (50.00%)	2 / 7 (28.57%)	
occurrences (all)	2	4	
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Anal erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Anal inflammation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Anal ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Constipation			

subjects affected / exposed	2 / 4 (50.00%)	4 / 7 (57.14%)	
occurrences (all)	2	4	
Faeces hard			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gingival erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Glossitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	5	
Pancreatitis acute			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Stomatitis			
subjects affected / exposed	2 / 4 (50.00%)	3 / 7 (42.86%)	
occurrences (all)	2	3	
Tongue ulceration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	4 / 7 (57.14%)	
occurrences (all)	1	10	
Oral disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hepatobiliary disorders			

Gallbladder oedema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hepatic steatosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Papule			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	3	
Pain of skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Eczema asteatotic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Dermatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Dry skin			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Rash erythematous			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	3	
Skin toxicity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	4	
Skin exfoliation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Rash papular			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Rash macular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 7 (14.29%)	
occurrences (all)	2	2	
Back pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	1	5	
Muscle spasms			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Myalgia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	1	3	
Infections and infestations			
Folliculitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Bacteraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	3	
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Disseminated mucormycosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Myringitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Oral infection			
subjects affected / exposed	0 / 4 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Parotitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	

Pneumonia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 7 (28.57%)	
occurrences (all)	2	8	
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	5	
Hyperlipidaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Hypermagnesaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Hyperphosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	3	2	
Hypertriglyceridaemia			
subjects affected / exposed	4 / 4 (100.00%)	2 / 7 (28.57%)	
occurrences (all)	9	6	
Hyperuricaemia			

subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	1	7	
Hypoalbuminaemia			
subjects affected / exposed	3 / 4 (75.00%)	4 / 7 (57.14%)	
occurrences (all)	12	8	
Hypocalcaemia			
subjects affected / exposed	3 / 4 (75.00%)	3 / 7 (42.86%)	
occurrences (all)	7	9	
Hypochloraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Hypokalaemia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 7 (42.86%)	
occurrences (all)	5	5	
Hypomagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	3 / 4 (75.00%)	2 / 7 (28.57%)	
occurrences (all)	7	6	
Hypophosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 7 (14.29%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2020	The following changes were made as per Amendment 1: 1. Updated the timing of EFS, PFS, and OS assessments, and end of treatment 1 (EOT1). 2. Removed peripheral blood samples for MRD. 3. Updated the exclusion criterion for current systemic use of any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 3A4 (CYP3A). 4. Updated procedures for recording and reporting adverse events and serious adverse events. 5. Added definition of relapse from CR.
23 February 2021	The following changes were made as per Amendment 2: 1. Removed a dose of asparaginase therapy given in combination with ponatinib. 2. Updated the projected duration of study. 3. Updated the number of study sites and countries. 4. Updated inclusion/exclusion criteria.
23 May 2023	The following changes were made as per Amendment 3: 1. Modified inclusion and exclusion criteria. 2. Defined the second cohort (cohort 2) of the phase 1 portion of the study. 3. Revised the disease assessment at end of reinduction and consolidation blocks. 4. Modified the medical management of elevated alanine aminotransferase. 5. Changed a secondary objective to an exploratory objective. 6. Corrected the schedule of events (SOEs) on which days the study treatment was administered. 7. Updated the definition of progression-free survival event for death.
02 November 2023	The following changes were made as per Amendment 4: 1. Modified Phase 1 cohort 2 to enroll a single cohort for determination of RP2D rather than 2 weight groups with separate evaluations. 2. Modified the definition of related adverse events for DLT. 3. Modified dose modifications for ponatinib with the occurrence of lipase elevations and pancreatitis. 4. Modified the criteria for beginning a consolidation block or optional continuation therapy. 5. Updated the number of participants in Phase 1 portion of the study. 6. Updated the minimum percentage and number of days of ponatinib dosing required for a participant to be evaluable for DLTs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 July 2024	The study enrollment was terminated per protocol due to DLTs observed in both dose cohorts in Phase 1 and the RP2D could not be determined leading to study termination by the Sponsor before Phase 2 could be initiated.	-

Notes:

Limitations and caveats

None reported