Clinical trial results:
Multicenter, Open-Label, Single Arm, Phase II Exploratory Study to Evaluate the Effect of a One-Year Consolidation Treatment with Ponatinib 15 mg on Treatment Free-Remission Rate in Patients with Philadelphia-Positive Chronic Myeloid Leukemia, who had previously Achieved a Deep Molecular Response with Imatinib

Summary

EudraCT number	2017-004565-27
Trial protocol	ES
Global end of trial date	29 April 2024

Results information

Result version number	v1 (current)
This version publication date	11 April 2025
First version publication date	11 April 2025
Summary attachment (see zip file)	PonaZero_Resúmen Resultados (PonaZero_Resúmen Resultados_REec.pdf)

Trial information

Trial identification

Sponsor protocol code	PonaZero_study

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	FUNDACIÓN TEÓFILO HERNANDO
Sponsor organisation address	Edificio las Rozas 23, planta S, oficina 1, Ctra. de La Coruña, km 23, 200, 28290 Las Rozas de Madr, Madrid, Spain, 28290
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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	20 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 June 2023
Global end of trial reached?	Yes
Global end of trial date	29 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the proportion of patients without confirmed loss of MR4 or loss of MMR (don’t require confirmation) within 48 weeks following ponatinib therapy cessation.

Protection of trial subjects:

1. The protocol and the informed consent were review and approved by the IEC of the Hospital Universitario de la Princesa (10/10/2018) and the AEMPS (15/11/2018).
2. Patients gave informed consent before the study began.
3. The clinical trials was conducted in accordance with the Declaration of Helsinki, GCP, and applicable regulatory requirements
4. The CRAs in charge of the trial periodically monitored that the study was conducted in accordance with the protocol and verified the accuracy and completeness of the data recorded in the eCRFs.
5. All patient information in this clinical trial was handled with the highest level of confidentiality. Patients were assigned a unique coded identifier (XX-XX) instead of using personal names to ensure their anonymity. This coding system was applied to all study-related documentation, including eCRFs, laboratory reports, and study databases.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	20
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment start date: 25/06/2019
Recruitment end date: 16/07/2021
Number of centers: 8
Patients recruited: 24 (center 2= 3; center 3= 1; center 4= 9; center 6= 1; center 8= 1, center 9= 4; center 10= 1; center 11= 4)

Pre-assignment

Screening details:

Number of subjects screened: 24
Number of screening failures: 1 did not meet the inclusion criteria (center 11)

Period 1

Period 1 title	Consolidation phase (48 weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single-arm

Arm description:

Patients that received ponatinib 15 mg during the consolidation phase

Arm type	Experimental
Investigational medicinal product name	Ponatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

15 mg once daily

Number of subjects in period 1[1]	Single-arm
Started	23
Consolidation phase	23
Completed	19
Not completed	4
Adverse event, non-fatal	3
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 24 patients were enrolled and 23 were included in the study as 1 patients was a screening failure.

Period 2	
Period 2 title	Treatment-Free Remission (96 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Single-arm
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Single-arm
Started	19
Completed	13
Not completed	6
Loss of molecular response	6

Baseline characteristics

Reporting groups

Reporting group title	Consolidation phase (48 weeks)

Reporting group description: -

Reporting group values	Consolidation phase (48 weeks)	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	52.8		
standard deviation	± 14.1	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	15	15	
Race Units: Subjects			
Caucasian	22	22	
Latin	1	1	
ECOG Units: Subjects			
0-zero	19	19	
1-one	4	4	
Physical examination - General Units: Subjects			
Normal	22	22	
Abnormal	1	1	
Physical examination - Skin Units: Subjects			
Normal	22	22	
Abnormal	1	1	
Physical examination - Neck Units: Subjects			
Normal	23	23	
Abnormal	0	0	

Physical examination - Ears Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Eyes Units: Subjects			
Normal	22	22	
Abnormal	1	1	
Physical examination - Nose Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Heart Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Throat Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Lungs Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Abdomen Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Back Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Lymph nodes Units: Subjects			
Normal	23	23	
Abrnomal	0	0	
Physical examination - Neurologic Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Extremities Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Vascular Units: Subjects			
Normal	23	23	
Abnormal	0	0	
Physical examination - Extramedular Units: Subjects			
Normal	23	23	

Abnormal	0	0	
Electrocardiogram Units: Subjects			
Normal	22	22	
Abnormal	1	1	
Echocardiogram Units: Subjects			
Normal	21	21	
Abnormal	2	2	
Pregnancy test Units: Subjects			
Negative	3	3	
Not applicable	20	20	
Hepatitis B surface antibody Units: Subjects			
Negative	15	15	
Positive	6	6	
No data	2	2	
Hepatitis B surface antigen Units: Subjects			
Negative	21	21	
Positive	0	0	
No data	2	2	
Hepatitis B core Units: Subjects			
Negative	19	19	
Positive	2	2	
No data	2	2	
Height Units: cm			
arithmetic mean	167.4		
standard deviation	± 9.3	-	
Weight Units: kg			
arithmetic mean	76.5		
standard deviation	± 12.0	-	
BMI Units: kg/m2			
arithmetic mean	27.4		
standard deviation	± 4.6	-	
Temperature Units: celsius temperature			
arithmetic mean	36.0		
standard deviation	± 0.4	-	
Respiratory rate Units: breaths per minute			
arithmetic mean	16.1		
standard deviation	± 2.1	-	
Systolic blood pressure Units: mmHg			
arithmetic mean	130.1		

standard deviation	± 22.6	-	
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	75.7		
standard deviation	± 12.9	-	
Pulse			
Units: lpm			
arithmetic mean	72.5		
standard deviation	± 10.7	-	
BCR-ABL molecular response			
Units: not applicable			
arithmetic mean	0.0016		
standard deviation	± 0.00	-	
Sokal risk			
Units: NA			
arithmetic mean	0.58		
standard deviation	± 0.3	-	
Hasford score			
Units: NA			
arithmetic mean	360.91		
standard deviation	± 351.6	-	
Eutos score			
Units: NA			
arithmetic mean	14.33		
standard deviation	± 17.4	-	
PR interval			
Units: ms			
arithmetic mean	144.6		
standard deviation	± 17.3	-	
QRS complex			
Units: ms			
arithmetic mean	98.9		
standard deviation	± 16.8	-	
QTcF interval			
Units: ms			
arithmetic mean	393.6		
standard deviation	± 63.4	-	
Heart rate			
Units: bpm			
arithmetic mean	69.0		
standard deviation	± 11.8	-	
RBC			
Units: x106/uL			
arithmetic mean	4.2		
standard deviation	± 0.5	-	
Hemoglobin			
Units: g/dL			
arithmetic mean	13.8		
standard deviation	± 1.3	-	
Hematocrit			
Units: percentage			
arithmetic mean	40.1		

standard deviation	± 4.1	-	
Platelets			
Units: x109			
arithmetic mean	235.5		
standard deviation	± 43.0	-	
Leucocytes			
Units: x109			
arithmetic mean	5.6		
standard deviation	± 1.6	-	
VCM			
Units: f/L			
arithmetic mean	95.0		
standard deviation	± 4.0	-	
Neutrophils absolute count			
Units: 109/L			
arithmetic mean	3.1		
standard deviation	± 1.1	-	
Neutrophils			
Units: percentage			
arithmetic mean	55.2		
standard deviation	± 8.7	-	
Lymphocytes			
Units: percentage			
arithmetic mean	32.4		
standard deviation	± 7.5	-	
Monocytes			
Units: percentage			
arithmetic mean	8.1		
standard deviation	± 1.9	-	
Eosinophils			
Units: percentage			
arithmetic mean	3.4		
standard deviation	± 2.4	-	
Basophils			
Units: percentage			
arithmetic mean	0.8		
standard deviation	± 0.4	-	
WBC			
Units: NA			
arithmetic mean	100.0		
standard deviation	± 0.2	-	
Glucose			
Units: mg/dL			
arithmetic mean	100.9		
standard deviation	± 9.9	-	
BUN			
Units: mg/dL			
arithmetic mean	32.4		
standard deviation	± 7.3	-	
Creatinine			
Units: mg/dL			
arithmetic mean	1.0		

standard deviation	± 0.2	-	
Albumin			
Units: g/dL			
arithmetic mean	5.9		
standard deviation	± 7.1	-	
AST			
Units: U/L			
arithmetic mean	21.9		
standard deviation	± 4.1	-	
ALT			
Units: U/L			
arithmetic mean	20.4		
standard deviation	± 8.4	-	
Alkaline phosphatase			
Units: UI/L			
arithmetic mean	68.8		
standard deviation	± 21.2	-	
Total billirubin			
Units: mg/dL			
arithmetic mean	0.5		
standard deviation	± 0.2	-	
Indirect billirubin			
Units: mg/dL			
arithmetic mean	0.5		
standard deviation	± 0.2	-	
Direct billirubin			
Units: mg/dL			
arithmetic mean	0.2		
standard deviation	± 0.1	-	
Troponin			
Units: ng/mL			
arithmetic mean	9.4		
standard deviation	± 5.9	-	
Troponin T			
Units: ng/mL			
arithmetic mean	10.3		
standard deviation	± 4.8	-	
NT-proBNP			
Units: pg/mL			
arithmetic mean	51.5		
standard deviation	± 57.5	-	
BNP			
Units: pg/mL			
arithmetic mean	113.8		
standard deviation	± 106.9	-	
Phosphorus			
Units: mg/dL			
arithmetic mean	2.7		
standard deviation	± 0.5	-	
Magnesium			
Units: mg/dL			
arithmetic mean	2.0		

standard deviation	± 0.1	-	
Soidum			
Units: mmol/L			
arithmetic mean	140.9		
standard deviation	± 2.0	-	
Potassium			
Units: mmol/L			
arithmetic mean	4.2		
standard deviation	± 0.3	-	
Calcium			
Units: mg/dL			
arithmetic mean	9.2		
standard deviation	± 0.4	-	
Amilase			
Units: U/L			
arithmetic mean	68.4		
standard deviation	± 25.2	-	
GGT			
Units: U/L			
arithmetic mean	20.6		
standard deviation	± 14.0	-	
LDH			
Units: U/L			
arithmetic mean	213.3		
standard deviation	± 46.3	-	
Lipase			
Units: U/L			
arithmetic mean	82.6		
standard deviation	± 72.1	-	
Total cholesterol			
Units: mg/dL			
arithmetic mean	175.7		
standard deviation	± 30.7	-	
Triglycerides			
Units: mg/dL			
arithmetic mean	113.7		
standard deviation	± 58.6	-	
HbA1c			
Units: percentage			
arithmetic mean	5.3		
standard deviation	± 0.3	-	
C-reactive protein			
Units: mg/dL			
arithmetic mean	0.3		
standard deviation	± 0.3	-	

Subject analysis sets

Subject analysis set title	TFR Phase Group
Subject analysis set type	Full analysis

Subject analysis set description:

Number of patients who entered ponatinib TFR phase

Subject analysis set title	Consolidation Phase Group
Subject analysis set type	Full analysis
Subject analysis set description: Patients who entered the Ponatinib consolidation phase	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least one dose of ponatinib	
Subject analysis set title	Patients who restarted TKI
Subject analysis set type	Full analysis
Subject analysis set description: Patients who lost molecular response and restart imatinib or any Tyrosine Kinase-Inhibitor treatment	

Reporting group values	TFR Phase Group	Consolidation Phase Group	Safety analysis set
Number of subjects	19	23	23
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	19	19
From 65-84 years	1	4	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female			
Male			
Race Units: Subjects			
Caucasian			
Latin			
ECOG Units: Subjects			
0-zero			
1-one			
Physical examination - General Units: Subjects			
Normal			
Abnormal			
Physical examination - Skin Units: Subjects			
Normal			
Abnormal			

Physical examination - Neck Units: Subjects			
Normal Abnormal			
Physical examination - Ears Units: Subjects			
Normal Abnormal			
Physical examination - Eyes Units: Subjects			
Normal Abnormal			
Physical examination - Nose Units: Subjects			
Normal Abnormal			
Physical examination - Heart Units: Subjects			
Normal Abnormal			
Physical examination - Throat Units: Subjects			
Normal Abnormal			
Physical examination - Lungs Units: Subjects			
Normal Abnormal			
Physical examination - Abdomen Units: Subjects			
Normal Abnormal			
Physical examination - Back Units: Subjects			
Normal Abnormal			
Physical examination - Lymph nodes Units: Subjects			
Normal Abrnomal			
Physical examination - Neurologic Units: Subjects			
Normal Abnormal			
Physical examination - Extremities Units: Subjects			
Normal Abnormal			
Physical examination - Vascular Units: Subjects			
Normal			

Abnormal			
Physical examination - Extramedular Units: Subjects			
Normal			
Abnormal			
Electrocardiogram Units: Subjects			
Normal			
Abnormal			
Echocardiogram Units: Subjects			
Normal			
Abnormal			
Pregnancy test Units: Subjects			
Negative			
Not applicable			
Hepatitis B surface antibody Units: Subjects			
Negative			
Positive			
No data			
Hepatitis B surface antigen Units: Subjects			
Negative			
Positive			
No data			
Hepatitis B core Units: Subjects			
Negative			
Positive			
No data			
Height Units: cm arithmetic mean standard deviation	±	±	±
Weight Units: kg arithmetic mean standard deviation	±	±	±
BMI Units: kg/m2 arithmetic mean standard deviation	±	±	±
Temperature Units: celsius temperature arithmetic mean standard deviation	±	±	±
Respiratory rate Units: breaths per minute arithmetic mean			

standard deviation	±	±	±
Systolic blood pressure Units: mmHg arithmetic mean standard deviation	±	±	±
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	±	±	±
Pulse Units: lpm arithmetic mean standard deviation	±	±	±
BCR-ABL molecular response Units: not applicable arithmetic mean standard deviation	±	±	±
Sokal risk Units: NA arithmetic mean standard deviation	±	±	±
Hasford score Units: NA arithmetic mean standard deviation	±	±	±
Eutos score Units: NA arithmetic mean standard deviation	±	±	±
PR interval Units: ms arithmetic mean standard deviation	±	±	±
QRS complex Units: ms arithmetic mean standard deviation	±	±	±
QTcF interval Units: ms arithmetic mean standard deviation	±	±	±
Heart rate Units: bpm arithmetic mean standard deviation	±	±	±
RBC Units: x106/uL arithmetic mean standard deviation	±	±	±
Hemoglobin Units: g/dL arithmetic mean			

standard deviation	±	±	±
Hematocrit Units: percentage arithmetic mean standard deviation	±	±	±
Platelets Units: x109 arithmetic mean standard deviation	±	±	±
Leucocytes Units: x109 arithmetic mean standard deviation	±	±	±
VCM Units: f/L arithmetic mean standard deviation	±	±	±
Neutrophils absolute count Units: 109/L arithmetic mean standard deviation	±	±	±
Neutrophils Units: percentage arithmetic mean standard deviation	±	±	±
Lymphocytes Units: percentage arithmetic mean standard deviation	±	±	±
Monocytes Units: percentage arithmetic mean standard deviation	±	±	±
Eosinophils Units: percentage arithmetic mean standard deviation	±	±	±
Basophils Units: percentage arithmetic mean standard deviation	±	±	±
WBC Units: NA arithmetic mean standard deviation	±	±	±
Glucose Units: mg/dL arithmetic mean standard deviation	±	±	±
BUN Units: mg/dL arithmetic mean			

standard deviation	±	±	±
Creatinine Units: mg/dL arithmetic mean standard deviation	±	±	±
Albumin Units: g/dL arithmetic mean standard deviation	±	±	±
AST Units: U/L arithmetic mean standard deviation	±	±	±
ALT Units: U/L arithmetic mean standard deviation	±	±	±
Alkaline phosphatase Units: UI/L arithmetic mean standard deviation	±	±	±
Total billirubin Units: mg/dL arithmetic mean standard deviation	±	±	±
Indirect billirubin Units: mg/dL arithmetic mean standard deviation	±	±	±
Direct billirubin Units: mg/dL arithmetic mean standard deviation	±	±	±
Troponin Units: ng/mL arithmetic mean standard deviation	±	±	±
Troponin T Units: ng/mL arithmetic mean standard deviation	±	±	±
NT-proBNP Units: pg/mL arithmetic mean standard deviation	±	±	±
BNP Units: pg/mL arithmetic mean standard deviation	±	±	±
Phosphorus Units: mg/dL arithmetic mean			

standard deviation	±	±	±
Magnesium Units: mg/dL arithmetic mean standard deviation	±	±	±
Soidum Units: mmol/L arithmetic mean standard deviation	±	±	±
Potassium Units: mmol/L arithmetic mean standard deviation	±	±	±
Calcium Units: mg/dL arithmetic mean standard deviation	±	±	±
Amilase Units: U/L arithmetic mean standard deviation	±	±	±
GGT Units: U/L arithmetic mean standard deviation	±	±	±
LDH Units: U/L arithmetic mean standard deviation	±	±	±
Lipase Units: U/L arithmetic mean standard deviation	±	±	±
Total cholesterol Units: mg/dL arithmetic mean standard deviation	±	±	±
Triglycerides Units: mg/dL arithmetic mean standard deviation	±	±	±
HbA1c Units: percentage arithmetic mean standard deviation	±	±	±
C-reactive protein Units: mg/dL arithmetic mean standard deviation	±	±	±

Reporting group values	Patients who restarted TKI		

Number of subjects	5		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	5		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical Units: Subjects			
Female			
Male			
Race Units: Subjects			
Caucasian			
Latin			
ECOG Units: Subjects			
0-zero			
1-one			
Physical examination - General Units: Subjects			
Normal			
Abnormal			
Physical examination - Skin Units: Subjects			
Normal			
Abnormal			
Physical examination - Neck Units: Subjects			
Normal			
Abnormal			
Physical examination - Ears Units: Subjects			
Normal			
Abnormal			
Physical examination - Eyes Units: Subjects			
Normal			
Abnormal			
Physical examination - Nose Units: Subjects			

Normal Abnormal			
Physical examination - Heart Units: Subjects			
Normal Abnormal			
Physical examination - Throat Units: Subjects			
Normal Abnormal			
Physical examination - Lungs Units: Subjects			
Normal Abnormal			
Physical examination - Abdomen Units: Subjects			
Normal Abnormal			
Physical examination - Back Units: Subjects			
Normal Abnormal			
Physical examination - Lymph nodes Units: Subjects			
Normal Abrnomal			
Physical examination - Neurologic Units: Subjects			
Normal Abnormal			
Physical examination - Extremities Units: Subjects			
Normal Abnormal			
Physical examination - Vascular Units: Subjects			
Normal Abnormal			
Physical examination - Extramedular Units: Subjects			
Normal Abnormal			
Electrocardiogram Units: Subjects			
Normal Abnormal			
Echocardiogram Units: Subjects			
Normal Abnormal			
Pregnancy test			

Units: Subjects			
Negative Not applicable			
Hepatitis B surface antibody Units: Subjects			
Negative Positive No data			
Hepatitis B surface antigen Units: Subjects			
Negative Positive No data			
Hepatitis B core Units: Subjects			
Negative Positive No data			
Height Units: cm arithmetic mean standard deviation	±		
Weight Units: kg arithmetic mean standard deviation	±		
BMI Units: kg/m2 arithmetic mean standard deviation	±		
Temperature Units: celsius temperature arithmetic mean standard deviation	±		
Respiratory rate Units: breaths per minute arithmetic mean standard deviation	±		
Systolic blood pressure Units: mmHg arithmetic mean standard deviation	±		
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	±		
Pulse Units: lpm arithmetic mean standard deviation	±		
BCR-ABL molecular response			

Units: not applicable arithmetic mean standard deviation	±		
Sokal risk Units: NA arithmetic mean standard deviation	±		
Hasford score Units: NA arithmetic mean standard deviation	±		
Eutos score Units: NA arithmetic mean standard deviation	±		
PR interval Units: ms arithmetic mean standard deviation	±		
QRS complex Units: ms arithmetic mean standard deviation	±		
QTcF interval Units: ms arithmetic mean standard deviation	±		
Heart rate Units: bpm arithmetic mean standard deviation	±		
RBC Units: x106/uL arithmetic mean standard deviation	±		
Hemoglobin Units: g/dL arithmetic mean standard deviation	±		
Hematocrit Units: percentage arithmetic mean standard deviation	±		
Platelets Units: x109 arithmetic mean standard deviation	±		
Leucocytes Units: x109 arithmetic mean standard deviation	±		
VCM			

Units: f/L arithmetic mean standard deviation	±		
Neutrophils absolute count Units: 109/L arithmetic mean standard deviation	±		
Neutrophils Units: percentage arithmetic mean standard deviation	±		
Lymphocytes Units: percentage arithmetic mean standard deviation	±		
Monocytes Units: percentage arithmetic mean standard deviation	±		
Eosinophils Units: percentage arithmetic mean standard deviation	±		
Basophils Units: percentage arithmetic mean standard deviation	±		
WBC Units: NA arithmetic mean standard deviation	±		
Glucose Units: mg/dL arithmetic mean standard deviation	±		
BUN Units: mg/dL arithmetic mean standard deviation	±		
Creatinine Units: mg/dL arithmetic mean standard deviation	±		
Albumin Units: g/dL arithmetic mean standard deviation	±		
AST Units: U/L arithmetic mean standard deviation	±		
ALT			

Units: U/L arithmetic mean standard deviation	±		
Alkaline phosphatase Units: UI/L arithmetic mean standard deviation	±		
Total billirubin Units: mg/dL arithmetic mean standard deviation	±		
Indirect billirubin Units: mg/dL arithmetic mean standard deviation	±		
Direct billirubin Units: mg/dL arithmetic mean standard deviation	±		
Troponin Units: ng/mL arithmetic mean standard deviation	±		
Troponin T Units: ng/mL arithmetic mean standard deviation	±		
NT-proBNP Units: pg/mL arithmetic mean standard deviation	±		
BNP Units: pg/mL arithmetic mean standard deviation	±		
Phosphorus Units: mg/dL arithmetic mean standard deviation	±		
Magnesium Units: mg/dL arithmetic mean standard deviation	±		
Soidum Units: mmol/L arithmetic mean standard deviation	±		
Potassium Units: mmol/L arithmetic mean standard deviation	±		
Calcium			

Units: mg/dL arithmetic mean standard deviation	±		
Amilase Units: U/L arithmetic mean standard deviation	±		
GGT Units: U/L arithmetic mean standard deviation	±		
LDH Units: U/L arithmetic mean standard deviation	±		
Lipase Units: U/L arithmetic mean standard deviation	±		
Total cholesterol Units: mg/dL arithmetic mean standard deviation	±		
Triglycerides Units: mg/dL arithmetic mean standard deviation	±		
HbA1c Units: percentage arithmetic mean standard deviation	±		
C-reactive protein Units: mg/dL arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	Single-arm
Reporting group description:	
Patients that received ponatinib 15 mg during the consolidation phase	
Reporting group title	Single-arm
Reporting group description: -	
Subject analysis set title	TFR Phase Group
Subject analysis set type	Full analysis
Subject analysis set description:	
Number of patients who entered ponatinib TFR phase	
Subject analysis set title	Consolidation Phase Group
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who entered the Ponatinib consolidation phase	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least one dose of ponatinib	
Subject analysis set title	Patients who restarted TKI
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who lost molecular response and restart imatinib or any Tyrosine Kinase-Inhibitor treatment	

Primary: Proportion of patients without confirmed loss of MR4 or MMR within 48 weeks after ponatinib TFR

End point title	Proportion of patients without confirmed loss of MR4 or MMR within 48 weeks after ponatinib TFR
End point description:	
The primary efficacy variable was the binary outcome measure, the proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks of ponatinib TFR. This variable was defined as the number of patients with no documented confirmed loss of MR4 or no loss of MMR and no restart of imatinib therapy in the first 48 weeks after the start of the ponatinib TFR phase divided by the number of patients who entered the ponatinib TFR phase (full analysis set).	
End point type	Primary
End point timeframe:	
From ponatinib discontinuation until 48 weeks of follow-up in TFR phase.	

End point values	Single-arm	TFR Phase Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: Proportion				
Without loss of molecular response	13	13		
Loss of molecular response	6	6		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Statistical analysis description:	
Primary Endpoint Analysis: Proportion of Patients Maintaining MR4/MMR at 48 Weeks Post-Ponatinib TFR	
Comparison groups	Single-arm v TFR Phase Group
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	Clopper-Pearson exact CI
Parameter estimate	Clopper-Pearson exact CI
Point estimate	0.684
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.434
upper limit	0.874

Notes:

[1] - Single-arm proportion analysis with Clopper-Pearson CI. IMPORTANT NOTE: This analysis was performed in the group of the patients who entered the TFR phase only (n=19).
[2] - Exact Clopper-Pearson confidence interval was used to assess the proportion of patients maintaining MR4/MMR at 48 weeks in TFR phase. The null hypothesis was rejected if the lower limit of the 95% confidence interval was greater than 0.10 (10%).

Secondary: Proportion of patients without documented loss of MR4 or loss of MMR at 72 and 96 weeks after ponatinib discontinuation

End point title	Proportion of patients without documented loss of MR4 or loss of MMR at 72 and 96 weeks after ponatinib discontinuation

End point description:

Proportion of patients without documented loss of MR4 or loss of MMR at 72 and 96 weeks after discontinuation of ponatinib treatment. This proportion of patients was calculated by dividing the number of patients with no documented confirmed loss of MR4 or loss of MMR and no reinitiation of imatinib at 72 or 96 weeks after discontinuation of ponatinib by the number of patients who entered the ponatinib TFR phase (full analysis set).

End point type	Secondary

End point timeframe:

From ponatinib discontinuation until 72 and 96 weeks of follow-up in TFR phase.

End point values	Single-arm	TFR Phase Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19[3]	19		
Units: Proportion				
Without loss of molecular response	13	13		
Loss molecular response	6	6		

Notes:

[3] - The number of patients who entered the TFR phase is 19.

Statistical analyses

Statistical analysis title	Analysis of TFR at 72 and 76 weeks

Statistical analysis description:

Analysis of Treatment-Free Remission (TFR) at 72 and 96 Weeks (visit 24 and 25, respectively)

Comparison groups	Single-arm v TFR Phase Group
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.05
Method	Clopper-Pearson exact CI
Parameter estimate	Clopper-Pearson exact CI
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.87

Notes:

[4] - Single-arm proportion analysis with Clopper-Pearson CI

Secondary: Progression-Free Survival (PFS) after ponatinib discontinuation

End point title	Progression-Free Survival (PFS) after ponatinib discontinuation

End point description:

Progression free survival (PFS): Estimation of PFS after discontinuation of ponatinib was calculated using the Kaplan-Meier (KM) method. PFS was measured from the date of discontinuation of ponatinib therapy to the date of the earliest of the following events: progression to AP/BC or death from any cause. For patients who are not known to have progressed or died on or before the cut-off date for the KM analysis, the PFS interval is right censored to the date of the last assessment of molecular response status or the cut-off date, whichever is earlier.

End point type	Secondary

End point timeframe:

From ponatinib discontinuation until progression to AP/BC, death, or last molecular response assessment before data cut-off

End point values	TFR Phase Group			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Number of patients	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-Free Survival (TFS) after ponatinib discontinuation

End point title	Treatment-Free Survival (TFS) after ponatinib discontinuation

End point description:

End point type	Secondary

End point timeframe:

From ponatinib discontinuation until loss of MMR, confirmed loss of MR4, restart of imatinib, progression to AP/BC, or death from any cause.

End point values	Single-arm	TFR Phase Group		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	19	19		
Units: Number of patients	15	15		

Statistical analyses

Statistical analysis title	Kaplan-Meier Estimation of TFS
Comparison groups	Single-arm v TFR Phase Group
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.05
Method	Kaplan-Meier survival analysis
Parameter estimate	Kaplan-Meier survival analysis
Point estimate	68.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.4
upper limit	92.9

Notes:

[5] - Kaplan-Meier survival analysis

Secondary: Overall Survival (OS) after ponatinib discontinuation

End point title	Overall Survival (OS) after ponatinib discontinuation

End point description:

Overall survival (OS): OS was defined as the time from the date of discontinuation of ponatinib therapy to the date of death from any cause. If a patient was not known to have died, OS was censored at the date of last contact (Figure 2). A similar method of analysis was used to estimate the time to regain MR4 from the date of restart of imatinib treatment.

End point type	Secondary

End point timeframe:

From ponatinib discontinuation until death from any cause or last patient contact (censored)

End point values	TFR Phase Group			
Subject group type	Subject analysis set			
Number of subjects analysed	19			
Units: Number of patients	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who regained MR4 within 48 weeks after imatinib re-initiation

End point title	Proportion of patients who regained MR4 within 48 weeks after imatinib re-initiation

End point description:

The proportion of patients who regained MR4 within 48 weeks of imatinib treatment re- initiation following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to ponatinib cessation, was calculated by dividing the number of patients who re-achieve MR4 within 48 weeks of imatinib treatment re-initiation, following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to ponatinib cessation, by the number of patients who ceased ponatinib therapy and subsequently had confirmed loss of MR4 or lost MMR in the first 48 weeks following ponatinib cessation and re-initiated imatinib treatment. In the calculation of this proportion, patients who dropped out early without regaining MR4 during the re-treatment period were considered to be unsuccessful reinductions of MR4 and were counted in the denominator in the calculation of the rate.

End point type	Secondary

End point timeframe:

From imatinib re-initiation until 48 weeks of follow-up

End point values	Patients who restarted TKI			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Proportion				
Regain molecular response	4			
Not regain molecular response	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma Concentration of Ponatinib Over Time

End point title	Plasma Concentration of Ponatinib Over Time

End point description:

End point type	Other pre-specified

End point timeframe:

rom Day 0 of Ponatinib Consolidation Phase until TFR Visit 11 (Day 28 of Cycle 1 in TFR phase)

End point values	Consolidation Phase Group			
Subject group type	Subject analysis set			
Number of subjects analysed	17[6]			
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	15.205 (10.030 to 20.431)			

Notes:

[6] - Number of patients at the visit 10 . Day 336 (end of treatment)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first ponatinib dose until study completion, categorized by phase: Consolidation phase, TFR phase, and Imatinib restart phase	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Consolidation phase
Reporting group description: AEs reported during the consolidation phase	
Reporting group title	TFR phase
Reporting group description: AEs reported during TFR	
Reporting group title	Imatinib restart
Reporting group description: AEs reported during imatinib restart period	

Serious adverse events	Consolidation phase	TFR phase	Imatinib restart
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Consolidation phase	TFR phase	Imatinib restart
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	19 / 19 (100.00%)	1 / 5 (20.00%)
Vascular disorders			
Essential hypertension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hypertension			
subjects affected / exposed	2 / 23 (8.70%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Intermittent claudication			

subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Superficial thrombophlebitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 23 (26.09%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	8	0	2
Chills			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Feeling cold			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Inflammation localized			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza-like illness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Pyrexia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Secretion discharge			

subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Nipple pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysphonia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Voice alteration			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Sleep disorder			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood iron increased			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood urinc acid increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyperuricemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Serum amylase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Serum lipase increased			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injection site inflammation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Subarachonoid hemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Traumatic pneumothorax			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Nervous system disorders			
Dizziness postural			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	3 / 23 (13.04%)	2 / 19 (10.53%)	0 / 5 (0.00%)
occurrences (all)	4	4	0
Paresthesia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sensory disturbance			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Leukocytosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Monocytosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Neutrophilia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Anal fissure			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Colitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	8 / 23 (34.78%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	8	0	0
Diarrhea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Diverticulosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Heartburn			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Ileal ulcer			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Mouth ulceration			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Periodontal disease			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pemphigoid			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	5 / 23 (21.74%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	6	0	0
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 23 (13.04%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Bone pain			
subjects affected / exposed	3 / 23 (13.04%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Bursitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1

Heaviness in extremities			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Intervertebral disc disorder			
subjects affected / exposed	2 / 23 (8.70%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Knee pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Lumbar pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Muscular weakness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	6 / 23 (26.09%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	6	1	0
Rib fracture			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Shoulder pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Spinal osteoarthritis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 23 (8.70%)	4 / 19 (21.05%)	0 / 5 (0.00%)
occurrences (all)	2	4	0
Common cold			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Localised infection			

subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oral infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	0 / 19 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypercholesterolemia			
subjects affected / exposed	3 / 23 (13.04%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Hypertriglyceridemia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 19 (5.26%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Hypomagnesemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Spinal flattening			
subjects affected / exposed	1 / 23 (4.35%)	0 / 19 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2019	- An error was found in the calculation of the total number of weeks with and without treatment with the study medication (being 28-day cycles, the correct number is 48 weeks per year instead of 52) that affects the primary and secondary objectives. - Discrepancies found between the study calendar tables and the protocol text. -Update of CTCAE from version 4.03 to 5.0 (has been released and will be used for the study).

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.

The study had a small sample size (23 patients), limiting generalizability. The single-arm design prevents direct comparisons with alternative treatment discontinuation strategies. The maximum follow-up was 96 weeks, which may not be sufficient.

Notes: