Clinical trial results:
An Open-Label, Randomized, Phase 2 Dose-Finding Study of Pacritinib in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated with Ruxolitinib

Summary

EudraCT number	2017-001772-28
Trial protocol	GB HU SE ES FR IT
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	19 December 2020
First version publication date	19 December 2020

Trial information

Trial identification

Sponsor protocol code	PAC203

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CTI BioPharma Corp
Sponsor organisation address	3101 Western Ave, Seattle, United States, 98121
Public contact	Regulatory Affairs-Sarah H. Telzrow, CTI BioPharma Corp., +1 2062724426, stelzrow@ctibiopharma.com
Scientific contact	Regulatory Affairs-Sarah H. Telzrow, CTI BioPharma Corp., +1 2062724426, stelzrow@ctibiopharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	17 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2018
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to explore the dose-response relationship for pacritinib among primary and secondary myelofibrosis (MF) patients to determine a recommended dosage for further clinical studies.

Protection of trial subjects:

The described study was performed in compliance with the Declaration of Helsinki, ICH guidelines, US Food and Drug Administration (FDA) regulations 21 CFR Parts 50, 56, and 312, and with the laws and regulations of the country in which the research was conducted, whichever afforded the greatest protection to the study patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	United States: 111
Worldwide total number of subjects	165
EEA total number of subjects	54

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)	44
From 65 to 84 years	118
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening procedures were completed between Days -35 and -7, before treatment initiation with the exception of the Screening (Baseline) MRI or CT scan, which was performed between Days -10 and -4.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pacritinib 100 mg QD

Arm description:

Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.

Arm type	Experimental
Investigational medicinal product name	Pacritinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pacritinib 100 mg (1 capsule) once daily (QD) orally, at the same time of day, with or without food during 24 weeks.

Arm title	Pacritinib 100 mg BID

Arm description:

Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.

Arm type	Experimental
Investigational medicinal product name	Pacritinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pacritinib 100 mg (1 capsule) twice daily (BID) orally, at the same time of day, with or without food during 24 weeks.

Arm title	Pacritinib 200 mg BID

Arm description:

Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.

Arm type	Experimental

Investigational medicinal product name	Pacritinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Pacritinib 200 mg (2 capsule) BID orally, at the same time of day, with or without food during 24 weeks.

Number of subjects in period 1[1]	Pacritinib 100 mg QD	Pacritinib 100 mg BID	Pacritinib 200 mg BID
Started	52	55	54
Completed	5	9	8
Not completed	47	46	46
Adverse event, serious fatal	4	3	3
Physician decision	23	17	23
Consent withdrawn by subject	11	7	6
Adverse event, non-fatal	2	8	7
Study Terminated By Sponsor	5	7	5
Death	1	1	-
Other	1	3	1
Lost to follow-up	-	-	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: A total of 165 were randomized in the trial, but only 161 subjects were included in the Full Analysis Population (FAP), this included all subjects who received at least 1 dose of study drug and had any efficacy measurements.

The discontinuations reasons are treated related only.

Baseline characteristics

Reporting groups	
Reporting group title	Pacritinib 100 mg QD
Reporting group description:	
Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.	
Reporting group title	Pacritinib 100 mg BID
Reporting group description:	
Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.	
Reporting group title	Pacritinib 200 mg BID
Reporting group description:	
Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.	

Reporting group values	Pacritinib 100 mg QD	Pacritinib 100 mg BID	Pacritinib 200 mg BID
Number of subjects	52	55	54
Age categorical			
The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study drug. Patients in this population were analyzed according to the treatment group to which they were assigned at randomization.			
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)	16	11	16
From 65-84 years	34	44	37
85 years and over	2	0	1
Gender categorical			
Units: Subjects			
Female	21	26	22
Male	31	29	32

Reporting group values	Total		
Number of subjects	161		
Age categorical			
The full analysis set (FAS) was defined as all randomized patients who received at least 1 dose of study drug. Patients in this population were analyzed according to the treatment group to which they were assigned at randomization.			
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)	43		
From 65-84 years	115		
85 years and over	3		
Gender categorical Units: Subjects			
Female	69		
Male	92		

End points

End points reporting groups

Reporting group title	Pacritinib 100 mg QD
Reporting group description:	
Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.	
Reporting group title	Pacritinib 100 mg BID
Reporting group description:	
Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.	
Reporting group title	Pacritinib 200 mg BID
Reporting group description:	
Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.	

Primary: Percent Reduction in Spleen Volume at Weeks 12 and 24

End point title	Percent Reduction in Spleen Volume at Weeks 12 and 24
End point description:	
The primary efficacy endpoint of this study was the percent reduction in spleen volume from baseline as measured by magnetic resonance imaging (MRI) or computed tomography (CT) at Weeks 12 and 24. Spleen volume at End of Treatment (EOT) was defined as the spleen volume collected at the EOT visit or the last spleen volume measured on treatment if not measured at EOT.	
End point type	Primary
End point timeframe:	
The primary efficacy endpoint was examined from baseline at Weeks 12, 24 and at EOT.	

End point values	Pacritinib 100 mg QD	Pacritinib 100 mg BID	Pacritinib 200 mg BID	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	55	54	
Units: Subjects	52	55	54	

Statistical analyses

Statistical analysis title	Spleen volume reduction (≥ 35%) - 100mg QD
Comparison groups	Pacritinib 100 mg BID v Pacritinib 100 mg QD v Pacritinib 200 mg BID
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Descriptive statistics - Percentages
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	6.8

Notes:

[1] - Statistical programming and analyses were performed using SAS® version 9.4.

Statistical analysis title	Spleen volume reduction (≥ 35%) - 100mg BID

Statistical analysis description:

To examine the dose-response relationship for efficacy, as measured by SVR using MRI (preferred) or CT and TSS using the MPN-SAF TSS 2.0

Comparison groups	Pacritinib 100 mg BID v Pacritinib 100 mg QD v Pacritinib 200 mg BID
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Descriptive statistics - Percentages
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	9.7

Statistical analysis title	Spleen volume reduction (≥ 35%) - 200mg BID
Comparison groups	Pacritinib 100 mg QD v Pacritinib 100 mg BID v Pacritinib 200 mg BID
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Descriptive statistics - Percentages
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	20.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected during the clinical study from the time the patient signed the informed consent through 30 days following last dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Pacritinib 100 mg QD

Reporting group description:

Patients with primary or secondary MF (Dynamic International Prognostic Scoring System [DIPSS] risk score of Intermediate-1 to High-Risk) who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.

Reporting group title	Pacritinib 100 mg BID

Reporting group description:

Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.

Reporting group title	Pacritinib 200 mg BID

Reporting group description:

Patients with primary or secondary MF who were previously treated with ruxolitinib. Patients included in this study previously failed therapy with ruxolitinib on the basis of intolerance or lack of efficacy.

Serious adverse events	Pacritinib 100 mg QD	Pacritinib 100 mg BID	Pacritinib 200 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 52 (36.54%)	20 / 55 (36.36%)	25 / 54 (46.30%)
number of deaths (all causes)	6	4	5
number of deaths resulting from adverse events	3	2	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myeloproliferative disorder			

subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pituitary tumour benign			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular compression			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	3 / 54 (5.56%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 52 (3.85%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Disease progression			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Drug withdrawal syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 52 (0.00%)	2 / 55 (3.64%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 52 (3.85%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypoxia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Transfusion reaction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Delayed haemolytic transfusion reaction			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incorrect drug administration duration			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Optic neuritis			

subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic infarction			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytosis			

subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			

subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal mass			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 52 (3.85%)	2 / 55 (3.64%)	5 / 54 (9.26%)
occurrences causally related to treatment / all	0 / 2	1 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 55 (1.82%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Tuberculosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 52 (1.92%)	2 / 55 (3.64%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes oesophagitis			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperuricaemia			

subjects affected / exposed	1 / 52 (1.92%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pacritinib 100 mg QD	Pacritinib 100 mg BID	Pacritinib 200 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 52 (90.38%)	51 / 55 (92.73%)	54 / 54 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 52 (5.77%)	1 / 55 (1.82%)	0 / 54 (0.00%)
occurrences (all)	3	1	0
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 52 (5.77%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences (all)	3	0	1
Hypertension			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	2 / 54 (3.70%)
occurrences (all)	0	4	2
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	9 / 52 (17.31%)	13 / 55 (23.64%)	13 / 54 (24.07%)
occurrences (all)	11	17	15
Oedema peripheral			
subjects affected / exposed	6 / 52 (11.54%)	5 / 55 (9.09%)	9 / 54 (16.67%)
occurrences (all)	7	5	11
Pyrexia			
subjects affected / exposed	6 / 52 (11.54%)	8 / 55 (14.55%)	5 / 54 (9.26%)
occurrences (all)	6	8	5
Chills			
subjects affected / exposed	5 / 52 (9.62%)	2 / 55 (3.64%)	4 / 54 (7.41%)
occurrences (all)	5	2	4
Non-cardiac chest pain			
subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	0 / 54 (0.00%)
occurrences (all)	3	2	0
Early satiety			
subjects affected / exposed	0 / 52 (0.00%)	1 / 55 (1.82%)	3 / 54 (5.56%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 52 (9.62%)	5 / 55 (9.09%)	6 / 54 (11.11%)
occurrences (all)	8	6	6
Epistaxis			
subjects affected / exposed	3 / 52 (5.77%)	4 / 55 (7.27%)	8 / 54 (14.81%)
occurrences (all)	3	6	13
Dyspnoea			
subjects affected / exposed	2 / 52 (3.85%)	7 / 55 (12.73%)	6 / 54 (11.11%)
occurrences (all)	2	8	7
Pleural effusion			
subjects affected / exposed	1 / 52 (1.92%)	2 / 55 (3.64%)	4 / 54 (7.41%)
occurrences (all)	1	2	4
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 52 (5.77%)	3 / 55 (5.45%)	7 / 54 (12.96%)
occurrences (all)	3	3	8
Investigations			

Weight decreased			
subjects affected / exposed	4 / 52 (7.69%)	1 / 55 (1.82%)	3 / 54 (5.56%)
occurrences (all)	4	1	5
Blood creatine increased			
subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	2 / 54 (3.70%)
occurrences (all)	3	2	2
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	4 / 54 (7.41%)
occurrences (all)	4	2	4
Platelet count decreased			
subjects affected / exposed	3 / 52 (5.77%)	3 / 55 (5.45%)	3 / 54 (5.56%)
occurrences (all)	3	4	5
Ejection fraction decreased			
subjects affected / exposed	2 / 52 (3.85%)	3 / 55 (5.45%)	2 / 54 (3.70%)
occurrences (all)	3	5	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
White blood cell count decreased			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	3 / 54 (5.56%)
occurrences (all)	0	4	5
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 52 (9.62%)	2 / 55 (3.64%)	5 / 54 (9.26%)
occurrences (all)	5	3	7
Fall			
subjects affected / exposed	4 / 52 (7.69%)	0 / 55 (0.00%)	1 / 54 (1.85%)
occurrences (all)	4	0	1
Nervous system disorders			
Memory impairment			
subjects affected / exposed	3 / 52 (5.77%)	0 / 55 (0.00%)	0 / 54 (0.00%)
occurrences (all)	3	0	0
Paraesthesia			
subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	1 / 54 (1.85%)
occurrences (all)	3	2	1
Dizziness			

subjects affected / exposed	2 / 52 (3.85%)	2 / 55 (3.64%)	5 / 54 (9.26%)
occurrences (all)	2	2	5
Headache			
subjects affected / exposed	2 / 52 (3.85%)	5 / 55 (9.09%)	2 / 54 (3.70%)
occurrences (all)	2	5	2
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	8 / 52 (15.38%)	8 / 55 (14.55%)	19 / 54 (35.19%)
occurrences (all)	13	10	31
Anaemia			
subjects affected / exposed	5 / 52 (9.62%)	5 / 55 (9.09%)	13 / 54 (24.07%)
occurrences (all)	5	7	19
Leukocytosis			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	0 / 54 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 52 (23.08%)	11 / 55 (20.00%)	15 / 54 (27.78%)
occurrences (all)	12	12	15
Diarrhoea			
subjects affected / exposed	10 / 52 (19.23%)	12 / 55 (21.82%)	16 / 54 (29.63%)
occurrences (all)	14	14	26
Abdominal pain			
subjects affected / exposed	9 / 52 (17.31%)	6 / 55 (10.91%)	13 / 54 (24.07%)
occurrences (all)	11	6	15
Vomiting			
subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	8 / 54 (14.81%)
occurrences (all)	3	2	8
Constipation			
subjects affected / exposed	2 / 52 (3.85%)	1 / 55 (1.82%)	10 / 54 (18.52%)
occurrences (all)	2	1	10
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	3 / 52 (5.77%)	1 / 55 (1.82%)	4 / 54 (7.41%)
occurrences (all)	3	1	5
Petechiae			

subjects affected / exposed	3 / 52 (5.77%)	2 / 55 (3.64%)	4 / 54 (7.41%)
occurrences (all)	3	2	5
Pruritus			
subjects affected / exposed	2 / 52 (3.85%)	10 / 55 (18.18%)	6 / 54 (11.11%)
occurrences (all)	2	12	6
Rash			
subjects affected / exposed	2 / 52 (3.85%)	3 / 55 (5.45%)	3 / 54 (5.56%)
occurrences (all)	2	5	3
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 52 (1.92%)	1 / 55 (1.82%)	4 / 54 (7.41%)
occurrences (all)	1	1	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 52 (7.69%)	1 / 55 (1.82%)	5 / 54 (9.26%)
occurrences (all)	5	1	5
Back pain			
subjects affected / exposed	2 / 52 (3.85%)	3 / 55 (5.45%)	5 / 54 (9.26%)
occurrences (all)	2	3	5
Pain in extremity			
subjects affected / exposed	2 / 52 (3.85%)	3 / 55 (5.45%)	3 / 54 (5.56%)
occurrences (all)	2	3	3
Musculoskeletal pain			
subjects affected / exposed	1 / 52 (1.92%)	3 / 55 (5.45%)	0 / 54 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 52 (7.69%)	3 / 55 (5.45%)	1 / 54 (1.85%)
occurrences (all)	7	3	1
Cellulitis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 55 (1.82%)	3 / 54 (5.56%)
occurrences (all)	1	1	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 52 (11.54%)	4 / 55 (7.27%)	10 / 54 (18.52%)
occurrences (all)	6	7	11

Fluid overload			
subjects affected / exposed	0 / 52 (0.00%)	0 / 55 (0.00%)	5 / 54 (9.26%)
occurrences (all)	0	0	5
Gout			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	4 / 54 (7.41%)
occurrences (all)	0	5	6
Hyperuricaemia			
subjects affected / exposed	0 / 52 (0.00%)	2 / 55 (3.64%)	3 / 54 (5.56%)
occurrences (all)	0	2	4
Hyponatraemia			
subjects affected / exposed	0 / 52 (0.00%)	3 / 55 (5.45%)	3 / 54 (5.56%)
occurrences (all)	0	4	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2017	•Timing changed for the first interim analysis to minimize treatment of patients with an ineffective dose •Randomization stratified by baseline platelet count & geographic region to ensure balance in risk factors between study arms •DNA samples collection to be used in future analyses to determine if specific mutations predict responsiveness to pacritinib • Screening visit window modified to support the investigator & site staff in the scheduling & performing of tests & assessments •Included additional changes required by the French,United Kingdom,Swedish & German regulatory bodies •Inclusion criteria changed to ensure that patients who enter the study had a documented adequate trial on ruxolitinib without demonstrated substantial efficacy •Revised text to define symptom control failure by the TSS instrument & ensure that only patients without adequate symptom control are eligible •Concomitant use of growth factor therapy prohibited •Corticosteroids to be used as supportive care for medically indicated conditions •Deleted dose re-escalation language as PAC203 is a dose-finding study •Added hemoglobin A1C & high sensitivity CRP tests to central laboratory analysis for future use as pharmacodynamics markers for pacritinib •Added modifications to specify that all prior experimental therapy requires a 28-day washout prior to randomization to ensure that drug associated AEs from prior therapy are identified & reported •Allowed patients to continue pacritinib after 24 weeks & define follow up assessments as evaluation of long-term safety of pacritinib is a secondary goal of the study •Deleted platelet count inclusion criterion to eliminate an impediment to enrollment not been shown to be associated with safety concerns •Added timing details for subsequent interim analyses to the first interim one •Deleted pacritinib dose reduction for patients requiring antiplatelet or anticoagulation agent to treat AEs •Allowed patients with platelets ≥ 100,000/µL
16 April 2018	• Expanded sample size to approximately 150 patients (up to 50 patients/arm) • Included additional dense PK blood sampling at selected sites for approximately 6 to 8 patients per treatment group • Specified a 30-minute window for the 0-hour (predose) PK & pharmacodynamics blood sampling • Specified that samples collected for unscheduled hematology & serum chemistry tests may be analyzed locally but must also be submitted to the central laboratory for testing & entry into the EDC • Excluded patients on high-dose ruxolitinib (more than 10 mg BID or 20 mg QD) who cannot tolerate tapering off ruxolitinib prior to the first dose of pacritinib • Removed the requirement for central radiographic confirmation of disease progression prior to stopping treatment
14 September 2018	• Revised study design to remove BPP interim futility analyses • Added text to require that if a grade 4 thrombocytopenia recurs after restarting drug, pacritinib must be discontinued per request from the French Competent Authority

06 May 2019	• Revised study design to terminate pacritinib treatment &study assessments at and beyond the Week 24 timepoint to conclude Phase 2 dose-finding study in preparation for Phase 3 • Added provision allowing patients who are benefiting from therapy, as of study drug termination, to continue receiving pacritinib under single patient expanded access or named patient programs at investigator discretion & subject to regulatory and IEC/IRB approval • Clarified that the FAS is defined as all randomized patients who received at least one dose of study drug. Remove reference to "Per Protocol Population."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported