Clinical trial results:
A Randomized Controlled Phase 3 Study of Oral Pacritinib versus Best Available Therapy in Patients with Thrombocytopenia and Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

Summary

EudraCT number	2013-004000-19
Trial protocol	BE GB DE HU CZ NL FR
Global end of trial date	26 April 2016

Results information

Result version number	v1 (current)
This version publication date	11 August 2018
First version publication date	11 August 2018

Trial information

Trial identification

Sponsor protocol code	PAC326

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02055781
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CTI Life Sciences Ltd.
Sponsor organisation address	Highlands House, Basingstoke Road, Spencers Wood, Reading, Berkshire, United Kingdom, RG7 1NT
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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	16 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the PERSIST-2 (PAC326) study was to compare the efficacy of pacritinib pooled once-daily (QD) and twice-daily (BID) dosing arms with that of BAT in subjects with thrombocytopenia and PMF, PPV-MF, or PET-MF. The efficacy co-primary endpoints for this analysis were the proportion of subjects achieving a ≥35% reduction in spleen volume from baseline to Week 24, as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan, and the proportion of subjects achieving a ≥50% reduction in TSS from baseline to Week 24 as measured by the MPN-SAF TSS 2.0.

Protection of trial subjects:

This trial was conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, US FDA regulations 21 Code of Federal Regulations Parts 50, 56, and 312, and with the laws and regulations of the country in which the research was conducted, whichever affords the greatest protection to the study subject.
No trial procedures were performed on trial participants until written consent had been obtained from them. The informed consent form (ICF), protocol, and amendments for this trial were submitted to and approved by the Ethics committee.
Routine monitoring was performed to verify that rights and well being of patients were protected. Also, any medication considered necessary for the patient’s safety and well-being was given at the discretion of the Investigator.

Background therapy:

Subjects received full supportive care, including transfusions of blood and blood products, antidiarrheal and antiemetic agents (see below), and antibiotics when appropriate. All concomitant medications and blood products administered during the subject’s participation in the study were recorded in the source documents and electronic case report forms (eCRFs).
Subjects did not receive other investigational agents during the study.

Evidence for comparator:

Given the increasing availability of ruxolitinib worldwide, and label guidance for treatment in patients with platelet counts between 50,000/µL and 100,000/µL at the time this study was initiated, ruxolitinib administered per package insert was included as a BAT treatment option. Placebo
control was deemed inappropriate for these patients, given the likelihood of efficacy given results of early phase pacritinib clinical studies, as well as the proven efficacy of the approved ruxolitinib agent, which also inhibits the JAK2 pathway.

Actual start date of recruitment	03 February 2014
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	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	United States: 131
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Russian Federation: 30
Worldwide total number of subjects	311
EEA total number of subjects	113

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)	105
From 65 to 84 years	203
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

311 patients from 12 countries (7 EU countries, Canada, USA, Russia, Australia and New Zealand) were enrolled. Enrolment started on 02 July 2014. Last patient visit was on 26 April 2016.

Pre-assignment

Screening details:

Participants had a study specific washout period (day -35 to day -7, depending on prior medication) and screening evaluations between day -14 to day -5 before entering treatment.

Period 1

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

Blinding implementation details:

With the exception of certain CTI personnel responsible for pharmacovigilance activities, regulatory submissions, supply chain, and quality, the sponsor and independent radiographic assessors were blinded to individual study treatment assignment until the end-of-treatment database was locked. Investigators, site personnel, subjects, clinical monitors, and a designated field CRA were unblinded throughout the duration of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pacritinib QD

Arm description:

Subjects in the pacritinib QD arm were treated with 400 mg pacritinib (4 capsules) once a day orally, at the same time of day, with or without food.
Subjects were supplied with 100 mg capsules of pacritinib for self-administration.

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

Dosage and administration details:

One capsule contains 100 mg pacritinib. Subjects who received pacritinib were to self-administer four 100 mg capsules per day orally, once a day (400 mg daily), at the same time of day, with or without food.

Arm title	Pacritinib BID

Arm description:

Subjects in the Pacritinib BID arm were treated with 200 mg pacritinib (2 capsules) twice each day orally, at the same time of day, with or without food.
Subjects were supplied with 100 mg capsules of pacritinib for self-administration.

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

Dosage and administration details:

One capsule contains 100 mg pacritinib. Subjects who received pacritinib were to self-administer two 100 mg capsules orally, twice per day (400 mg daily), at the same time of day, with or without food.

Arm title	Best available Therapies (BAT)

Arm description:

Best available Therapies (BAT): Subjects receiving BAT were treated on a schedule commensurate with the therapy or therapies chosen by the investigator. BAT agents could be administered as monotherapy or in combinations, and could be changed (eg, new dose, new schedule, new regimen) as clinically indicated without limitation.
BAT therapies included any physician-selected treatment for PMF, PPV-MF, or PET-MF, including approved JAK inhibitors, and may have included any treatment received before study entry. BAT agents also could have included no treatment (watch and wait, except in Czech Republic) or symptomdirected treatment without MF-specific treatment. Best available therapies could not be coadministered to pacritinib patients for treatment of MF.

Arm type	Active comparator
Investigational medicinal product name	PMF, PPV-MF, or PET-MF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Physician’s choice of treatment for PMF, PPV-MF, or PET-MF on a schedule commensurate with the chosen treatment. Ruxolitinib was required to be administered
according to package insert for patients with thrombocytopenia.

Number of subjects in period 1	Pacritinib QD	Pacritinib BID	Best available Therapies (BAT)
Started	104	107	100
Completed	62	79	63
Not completed	42	28	37
Adverse event, serious fatal	22	20	19
Physician decision	6	1	3
Consent withdrawn by subject	8	2	8
other	6	5	7

Baseline characteristics

Reporting groups	
Reporting group title	Pacritinib QD
Reporting group description:	
Subjects in the pacritinib QD arm were treated with 400 mg pacritinib (4 capsules) once a day orally, at the same time of day, with or without food. Subjects were supplied with 100 mg capsules of pacritinib for self-administration.	
Reporting group title	Pacritinib BID
Reporting group description:	
Subjects in the Pacritinib BID arm were treated with 200 mg pacritinib (2 capsules) twice each day orally, at the same time of day, with or without food. Subjects were supplied with 100 mg capsules of pacritinib for self-administration.	
Reporting group title	Best available Therapies (BAT)
Reporting group description:	
Best available Therapies (BAT): Subjects receiving BAT were treated on a schedule commensurate with the therapy or therapies chosen by the investigator. BAT agents could be administered as monotherapy or in combinations, and could be changed (eg, new dose, new schedule, new regimen) as clinically indicated without limitation. BAT therapies included any physician-selected treatment for PMF, PPV-MF, or PET-MF, including approved JAK inhibitors, and may have included any treatment received before study entry. BAT agents also could have included no treatment (watch and wait, except in Czech Republic) or symptomdirected treatment without MF-specific treatment. Best available therapies could not be coadministered to pacritinib patients for treatment of MF.	

Reporting group values	Pacritinib QD	Pacritinib BID	Best available Therapies (BAT)
Number of subjects	104	107	100
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)	32	41	32
From 65-84 years	70	65	68
85 years and over	2	1	0
Age continuous Units: years			
arithmetic mean	69.0	65.9	66.9
standard deviation	± 8.55	± 8.75	± 9.75
Gender categorical Units: Subjects			
Female	51	44	45
Male	53	63	55
Race Units: Subjects			
White	90	92	85
Not reported	9	10	8
Asian	3	3	4

Native Hawaiian / Other Pacific Islander	1	2	1
American Indian / Alaska Native	0	0	1
Black / African American	1	0	0
Other	0	0	1

Reporting group values	Total		
Number of subjects	311		
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)	105		
From 65-84 years	203		
85 years and over	3		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	140		
Male	171		
Race			
Units: Subjects			
White	267		
Not reported	27		
Asian	10		
Native Hawaiian / Other Pacific Islander	4		
American Indian / Alaska Native	1		
Black / African American	1		
Other	1		

End points

End points reporting groups

Reporting group title	Pacritinib QD

Reporting group description:

Subjects in the pacritinib QD arm were treated with 400 mg pacritinib (4 capsules) once a day orally, at the same time of day, with or without food.
Subjects were supplied with 100 mg capsules of pacritinib for self-administration.

Reporting group title	Pacritinib BID

Reporting group description:

Subjects in the Pacritinib BID arm were treated with 200 mg pacritinib (2 capsules) twice each day orally, at the same time of day, with or without food.
Subjects were supplied with 100 mg capsules of pacritinib for self-administration.

Reporting group title	Best available Therapies (BAT)

Reporting group description:

Best available Therapies (BAT): Subjects receiving BAT were treated on a schedule commensurate with the therapy or therapies chosen by the investigator. BAT agents could be administered as monotherapy or in combinations, and could be changed (eg, new dose, new schedule, new regimen) as clinically indicated without limitation.
BAT therapies included any physician-selected treatment for PMF, PPV-MF, or PET-MF, including approved JAK inhibitors, and may have included any treatment received before study entry. BAT agents also could have included no treatment (watch and wait, except in Czech Republic) or symptomdirected treatment without MF-specific treatment. Best available therapies could not be coadministered to pacritinib patients for treatment of MF.

Subject analysis set title	Pacritinib QD - ITT Efficacy
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

ITT truncated on the day of the FDA clinical hold, i.e., patients randomized prior to September 7, 2015.

Subject analysis set title	Pacritinib BID - ITT Efficacy
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

ITT truncated on the day of the FDA clinical hold, i.e., patients randomized prior to September 7, 2015

Subject analysis set title	Best available Therapies (BAT) - ITT Efficacy
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

ITT truncated on the day of the FDA clinical hold, i.e., patients randomized prior to September 7, 2015

Subject analysis set title	Pacritinib QD + BID - ITT Efficacy
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

ITT truncated on the day of the FDA clinical hold, i.e., patients randomized prior to September 7, 2015.
Pooled from the Pacritinib QD - ITT Efficacy and Pacritinib BID - ITT Efficacy population.

Primary: ≥35% Spleen Volume Reduction

End point title	≥35% Spleen Volume Reduction

End point description:

The first co-primary efficacy endpoint was the proportion of subjects achieving a ≥35% spleen volume reduction (SVR) from baseline to Week 24, as measured by MRI or CT scan.

End point type	Primary

End point timeframe:

MRI or CT scan (without contrast agents) was performed prior to randomization (days -10 to -4). MRI or CT scan was performed at the end of week 12 ± 7 days and every 12 weeks thereafter, and at treatment termination.

End point values	Pacritinib QD - ITT Efficacy	Pacritinib BID - ITT Efficacy	Best available Therapies (BAT) - ITT Efficacy	Pacritinib QD + BID - ITT Efficacy
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	75	74	72	149
Units: patient number (n)				
Overall (n)	11	16	2	27

Statistical analyses

Statistical analysis title	Primary endpoint statistics
Comparison groups	Best available Therapies (BAT) - ITT Efficacy v Pacritinib QD + BID - ITT Efficacy
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [1]
Method	Fisher exact
Parameter estimate	Agresti-Caffo method
Point estimate	15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.8
upper limit	22.1

Notes:

[1] - BAT arm compared to pooled pacritinib arms (Pacritinib QD + BID - ITT Efficacy)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were collected during the clinical trial from the time the subject signed the informed consent through the subject's last day of study participation.

Adverse event reporting additional description:

The data display threshold for SAEs is set to 1% or more, that of AEs is set to 5% or more.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Best available Therapy (BAT) - Safety

Reporting group description:

The safety population was defined as all randomized subjects who received at least one dose of study treatment, including subjects on the BAT arm who were not receiving any active study treatment (watchful waiting). All safety analyses were performed using the safety population, and subjects in this population were analyzed according to the treatment actually received.

Reporting group title	Pacritinib (QD and BID) - Safety

Reporting group description:

The safety population was defined as all randomized subjects who received at least one dose of study treatment, including subjects on the BAT arm who were not receiving any active study treatment (watchful waiting). All safety analyses were performed using the safety population, and subjects in this population were analyzed according to the treatment actually received.

Serious adverse events	Best available Therapy (BAT) - Safety	Pacritinib (QD and BID) - Safety	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 100 (71.00%)	91 / 211 (43.13%)	
number of deaths (all causes)	9	12	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	2 / 100 (2.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 100 (0.00%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myeloid leukaemia			

subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myelofibrosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	3 / 100 (3.00%)	7 / 211 (3.32%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 3	1 / 7	
Pyrexia			
subjects affected / exposed	2 / 100 (2.00%)	5 / 211 (2.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed	1 / 100 (1.00%)	4 / 211 (1.90%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 100 (1.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Ankle fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 100 (2.00%)	5 / 211 (2.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 100 (3.00%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neurological decompensation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Transient ischaemic attack			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 100 (3.00%)	13 / 211 (6.16%)	
occurrences causally related to treatment / all	1 / 3	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 100 (2.00%)	8 / 211 (3.79%)	
occurrences causally related to treatment / all	1 / 2	4 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
Febrile neutropenia			
subjects affected / exposed	2 / 100 (2.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	0 / 100 (0.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rash			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 100 (2.00%)	7 / 211 (3.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Periarthritis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 100 (4.00%)	11 / 211 (5.21%)	
occurrences causally related to treatment / all	0 / 4	2 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 100 (0.00%)	3 / 211 (1.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 100 (1.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Sepsis			
subjects affected / exposed	1 / 100 (1.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 100 (2.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 100 (1.00%)	1 / 211 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	1 / 100 (1.00%)	2 / 211 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fluid overload			
subjects affected / exposed	1 / 100 (1.00%)	0 / 211 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Best available Therapy (BAT) - Safety	Pacritinib (QD and BID) - Safety	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	87 / 100 (87.00%)	204 / 211 (96.68%)	
Investigations			
Weight decreased			
subjects affected / exposed	3 / 100 (3.00%)	11 / 211 (5.21%)	
occurrences (all)	3	11	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	8 / 100 (8.00%)	17 / 211 (8.06%)	
occurrences (all)	8	17	
Fall			
subjects affected / exposed	3 / 100 (3.00%)	11 / 211 (5.21%)	
occurrences (all)	3	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 100 (5.00%)	31 / 211 (14.69%)	
occurrences (all)	5	31	
Dysgeusia			
subjects affected / exposed	0 / 100 (0.00%)	16 / 211 (7.58%)	
occurrences (all)	0	16	
Headache			
subjects affected / exposed	5 / 100 (5.00%)	15 / 211 (7.11%)	
occurrences (all)	5	15	
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	22 / 100 (22.00%)	65 / 211 (30.81%)	
occurrences (all)	22	65	
Anaemia			
subjects affected / exposed	13 / 100 (13.00%)	48 / 211 (22.75%)	
occurrences (all)	13	48	
Neutropenia			
subjects affected / exposed	5 / 100 (5.00%)	17 / 211 (8.06%)	
occurrences (all)	5	17	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 100 (16.00%)	35 / 211 (16.59%)	
occurrences (all)	16	35	
Oedema peripheral			
subjects affected / exposed	14 / 100 (14.00%)	35 / 211 (16.59%)	
occurrences (all)	14	35	
Asthenia			
subjects affected / exposed	6 / 100 (6.00%)	8 / 211 (3.79%)	
occurrences (all)	6	8	
Early satiety			
subjects affected / exposed	5 / 100 (5.00%)	4 / 211 (1.90%)	
occurrences (all)	5	4	
Pyrexia			
subjects affected / exposed	1 / 100 (1.00%)	22 / 211 (10.43%)	
occurrences (all)	1	22	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 100 (15.00%)	121 / 211 (57.35%)	
occurrences (all)	15	121	
Nausea			
subjects affected / exposed	11 / 100 (11.00%)	73 / 211 (34.60%)	
occurrences (all)	11	73	
Vomiting			
subjects affected / exposed	5 / 100 (5.00%)	42 / 211 (19.91%)	
occurrences (all)	5	42	
Abdominal pain			

subjects affected / exposed	19 / 100 (19.00%)	29 / 211 (13.74%)	
occurrences (all)	19	29	
Abdominal distension			
subjects affected / exposed	6 / 100 (6.00%)	9 / 211 (4.27%)	
occurrences (all)	6	9	
Abdominal pain upper			
subjects affected / exposed	6 / 100 (6.00%)	10 / 211 (4.74%)	
occurrences (all)	6	10	
Constipation			
subjects affected / exposed	6 / 100 (6.00%)	23 / 211 (10.90%)	
occurrences (all)	6	23	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	12 / 100 (12.00%)	23 / 211 (10.90%)	
occurrences (all)	12	23	
Cough			
subjects affected / exposed	10 / 100 (10.00%)	19 / 211 (9.00%)	
occurrences (all)	10	19	
Dyspnoea			
subjects affected / exposed	8 / 100 (8.00%)	19 / 211 (9.00%)	
occurrences (all)	8	19	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 100 (6.00%)	21 / 211 (9.95%)	
occurrences (all)	6	21	
Rash			
subjects affected / exposed	4 / 100 (4.00%)	14 / 211 (6.64%)	
occurrences (all)	4	14	
Night sweats			
subjects affected / exposed	6 / 100 (6.00%)	16 / 211 (7.58%)	
occurrences (all)	6	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 100 (4.00%)	22 / 211 (10.43%)	
occurrences (all)	4	22	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 100 (3.00%)	17 / 211 (8.06%)	
occurrences (all)	3	17	
Bone pain			
subjects affected / exposed	7 / 100 (7.00%)	12 / 211 (5.69%)	
occurrences (all)	7	12	
Pain in extremity			
subjects affected / exposed	6 / 100 (6.00%)	17 / 211 (8.06%)	
occurrences (all)	6	17	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 100 (6.00%)	19 / 211 (9.00%)	
occurrences (all)	6	19	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	10 / 100 (10.00%)	25 / 211 (11.85%)	
occurrences (all)	10	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2014	The changes included: - Inconsistencies between the protocol and the schedule of assessments regarding pacritinib accountability were corrected. - A clarification regarding the pharmacodynamic assessment was added. - Inconsistencies regarding the timing of the administration of the patient global impression assessment, MPN-SAF TSS, pain medication log and quality of life assessments were clarified and/or corrected. - A detailed QTc monitoring schedule was added. - The definition of a serious adverse event was updated. - The reference safety information was further specified.
31 July 2014	The changes included: - The exclusion criterion of more than 6 months of cumulative prior JAK2 inhibitor treatment was deleted.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 February 2016	The FDA placed the pacritinib IND on partial clinical hold on 2016 February 04, then on full clinical hold on 2016 February 08. All subjects were notified of the clinical holds and instructed to discontinue pacritinib treatment immediately. Subjects returned to the clinic for termination and 30-day post-termination visits per schedule of assessments . Data entry and verification were completed and the end of treatment database was locked.	-

Notes:

Limitations and caveats

None reported