Clinical trial results:
A UK open-label, multicentre, exploratory Phase II study of INC424 for patients with primary myelofibrosis (PMF) or post polycythemia myelofibrosis (PPV MF) or post-essential thrombocythemia myelofibrosis (PET-MF)

Summary

EudraCT number	2011-005066-38
Trial protocol	GB
Global end of trial date	28 January 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	16 August 2015

Trial information

Trial identification

Sponsor protocol code	CINC424AGB02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01558739
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,

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	28 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of daily oral doses of 15mg BID or 20mg BID of INC424 in patients with PMF, PPV-MF, or PET-MF, based on the proportion of patients experiencing treatment success at the 48 week timepoint. Treatment success was defined as:
- 50% or greater reduction in palpable spleen length versus Baseline at the 48-week time point and/or
- 50% or greater improvement in total symptom scores (derived from MF symptom assessment form [MFSAF] questionnaire) versus Baseline at the 48-week time point

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	15
From 65 to 84 years	31
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Fifty-four patients were screened. Forty-eight subjects were enrolled. All sites were in the United Kingdom.

Pre-assignment

Screening details:

Screening details:
Screening period duration was Day - 28 to Day -1.
Fifty-four patients were screened and 6 were discontinued: 4 for unacceptable test procedure result, 1 withdrew consent, and 1 for "other".

Period 1

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

Arms

Arm title	Oral INC424 at a dose of 15 or 20 mg twice daily

Arm description:

Patients diagnosed with PMF, PPV MF, or PET-MF were treated with oral INC424 at a dose of 15 - 20 mg (dose based on Baseline platelet count) twice daily.

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose (Patients with platelet counts less than 100,000 L were ineligible for the study):
- Patients with a Baseline platelet count of > 200,000/µL began dosing at 20 mg per os (p.o.) BID (four 5 mg tablets BID).
- Patients with a Baseline platelet count between 100,000 – 200,000/µL (inclusive) began dosing at 15 mg p.o. BID (three 5 mg tablets BID).

Dose could be increased by 5 mg BID (for optimization of dosing) after at least Week 4 (Month 1) for patients who met all of the following conditions:
- Palpable spleen length below the costal margin that decreased by less than 40% at the Week 4 visit relative to Baseline.
- Platelet count at the Week 4 blood draw was > 150,000/µL and platelet count had never been below 150,000/µL at a prior laboratory evaluation while receiving ruxolitinib.
- ANC levels had remained at or above 1000/µL since enrollment in the study.
Guidance was provided for decreasing, interruption or discontinuation of study drug.

Number of subjects in period 1	Oral INC424 at a dose of 15 or 20 mg twice daily
Started	48
Completed	31
Not completed	17
Consent withdrawn by subject	2
Adverse event, non-fatal	7
Death	3
Lack of efficacy	4
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description:

Patients diagnosed with PMF, PPV MF, or PET-MF were treated with oral INC424 at a dose of 15 - 20 mg (dose based on Baseline platelet count) twice daily.

Reporting group values	Treatment	Total	
Number of subjects	48	48	
Age categorical Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	31	31	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female	21	21	
Male	27	27	

Subject analysis sets

Subject analysis set title	Full Analysis Set and Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis set (FAS) consisted of all patients who received at least one administration of study drug and had at least one post-Baseline efficacy assessment.

The Safety set consisted of all patients who received at least one dose of study drug and had at least one post-Baseline safety assessment. The statement that a patient had no AEs constituted a safety assessment. Patients who had received at least one dose of study drug but who had no post-treatment safety data of any kind were be excluded from the safety population.

Reporting group values	Full Analysis Set and Safety Set		
Number of subjects	48		
Age categorical Units: Subjects			
Adults (18-64 years)	15		
From 65-84 years	31		
85 years and over	2		
Gender categorical Units: Subjects			
Female	21		
Male	27		

End points

End points reporting groups

Reporting group title	Oral INC424 at a dose of 15 or 20 mg twice daily

Reporting group description:

Patients diagnosed with PMF, PPV MF, or PET-MF were treated with oral INC424 at a dose of 15 - 20 mg (dose based on Baseline platelet count) twice daily.

Subject analysis set title	Full Analysis Set and Safety Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis set (FAS) consisted of all patients who received at least one administration of study drug and had at least one post-Baseline efficacy assessment.

The Safety set consisted of all patients who received at least one dose of study drug and had at least one post-Baseline safety assessment. The statement that a patient had no AEs constituted a safety assessment. Patients who had received at least one dose of study drug but who had no post-treatment safety data of any kind were be excluded from the safety population.

Primary: Percentage of Participants With Treatment Success at Week 48

End point title	Percentage of Participants With Treatment Success at Week

End point description:

Treatment success was defined as a 50% or greater reduction in palpable spleen length versus baseline at 48 weeks and/or a 50% or greater improvement in total symptom score (derived from the MF symptom assessment form (MFSAF) questionnaire) versus baseline at the week 48 time point. The MFSAF assesses the following symptoms (all scored from absent (0) to worst imaginable (10)): general fatigue, abdominal pain (and discomfort), inactivity (ability to move and walk around), cough, night sweats, itching (pruritus), bone pain (diffuse not joint pain or arthritis), fever, change in appetite/unintentional weight loss (or gain) in past 6 months, overall quality of life (QoL).

Full analysis set (FAS): The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Primary

End point timeframe:

Baseline versus 48 week end of treatment.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary objective of the study was to provide an estimate of the ability of daily oral doses of 15 or 20 mg BID of ruxolitinib to produce treatment success in patients with PMF, PPV MF or PET-MF at Week 48.
Analysis focused on estimation (point estimate together with 95% confidence interval [CI]). The proportion of patients with treatment response at Week 48 was estimated using an exact (Clopper-Pearson) 95% CI. No statistical hypothesis testing done.

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of Patients				
number (not applicable)				
Percentage of Participants With Treatment Success	50			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Best Overall Response

End point title	Percentage of Participants With Best Overall Response

End point description:

Response to treatment and disease progression was assessed by physical examination, specifically assessing changes in spleen size by palpation. Disease response and progression was evaluated using the International Working Group for myelofibrosis Research and Treatment Response Criteria.

Only participants from the full analysis set (FAS), who had evaluable measurements at both baseline and the post-baseline week time point, was included in the analysis for that time point. The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Week 48.

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of Participants				
number (not applicable)				
Clinical improvement	6.3			
Complete response	6.3			
Partial response	39.6			
Stable disease	47.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Myelofibrosis Symptoms Assessment Form (MF-SAF)

End point title	Change From Baseline in Myelofibrosis Symptoms Assessment Form (MF-SAF)

End point description:

The MF-SAF consists of seven questions about key symptoms and impact of MF. Questions are scored on a scale of 0–10, with higher scores indicating more severe symptoms and greater inactivity. Questions 1–6, which together comprise a Total Symptom Score (TSS), investigate the following symptoms: night

sweats, pruritus/itching, abdominal discomfort, pain under the ribs, early satiety and bone/muscle pain. Question 7 asks patients to report levels of inactivity. The TSS reflects the sum of the scores of these symptoms excluding inactivity, with the maximum possible score being 60 (most severe symptom experienced).

Only participants from the full analysis set (FAS), who had evaluable measurements at both baseline and the post-baseline week time point, was included in the analysis for that time point. The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline, week 4, week 12, week 24, week 48

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=37)	-8.78 (± 10.638)			
Week 12 (n=35)	-8.46 (± 12.871)			
Week 24 (n=30)	-9.13 (± 11.95)			
Week 48 (n=18)	-7.83 (± 9.966)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ5D Preference Index (5 Level EuroQol Questionnaire Determining Quality of Life) From Baseline

End point title	Change From Baseline in EQ5D Preference Index (5 Level EuroQol Questionnaire Determining Quality of Life) From Baseline

End point description:

The EQ-5D is a standardized instrument used for measuring health outcomes in a wide range of health conditions and treatment. It consists of a descriptive system and a visual analogue scale (EQ-VAS). The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The EQ-VAS records the participant's self-rated health on a vertical, VAS where the endpoints are labeled 'best imaginable health state' and 'worst imaginable health state'. The EQ-5D health state was converted to a single summary index by applying a formula that attaches a weight to each of the levels in each dimension. The final EQ5D preference index scores range from 0 to 1 with higher scores indicating better health.
Only participants from the full analysis set (FAS), who had evaluable measurements at both baseline and the post-baseline week time point, was included in

End point type	Secondary

End point timeframe:

Baseline, week 4, week 12, week 24, week 48

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Index score				
arithmetic mean (standard deviation)				
Week 4 (n=40)	0.06 (± 0.173)			
Week 12 (n=38)	0.05 (± 0.178)			
Week 24 (n=34)	0.05 (± 0.231)			
Week 48 (n=29)	0.03 (± 0.222)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospitalizations

End point title	Number of Hospitalizations

End point description:

Medical resource utilization (MRU) was assessed according to the number of hospitalizations.

Only participants from the full analysis set (FAS), who had evaluable measurements at the post-baseline week time point, were included in the analysis for that time point. The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

week 12, week 24, week 26, week 48

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Number of Hospitalizations				
arithmetic mean (standard deviation)				
Week 12 (n=48)	0.1 (± 0.371)			
Week 24 (n=40)	0.03 (± 0.158)			
Week 36 (n=37)	0.05 (± 0.229)			
Week 48 (n=35)	0.09 (± 0.284)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalizations

End point title	Duration of Hospitalizations

End point description:

MRU was assessed according to the mean duration of hospitalization visits.

Participants from the full analysis set, who were hospitalized between baseline and week 48, were included in the analysis.

End point type	Secondary

End point timeframe:

Week 48

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Duration of days hospitalized				
arithmetic mean (standard deviation)				
Duration of Hospitalizations (days)	9 (± 5.852)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Accident & Emergency Visits From Baseline

End point title	Number of Accident & Emergency Visits From Baseline

End point description:

MRU was assessed according to the number of accidents and emergency room visits

Only participants from the full analysis set (FAS), who had evaluable measurements at each timeframe, e.g. from baseline to week 12, were included in the analysis for that timeframe. The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

baseline to week 12, week 12 to week 24, week 24 to week 36, week 36 to week 48

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Accident and Emergency Visits from Base				
median (full range (min-max))				
Baseline to week 12 (n=48)	0 (0 to 2)			
Week 12 to week 24 (n=39)	0 (0 to 1)			
Week 24 to week 36 (n=33)	0 (0 to 2)			
Week 36 to week 48 (n=33)	0 (0 to 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Transfusion Dependency Status

End point title	Percentage of Participants With Transfusion Dependency Status

End point description:

Transfusion dependency status from baseline through the end of study was assessed. New onset of transfusion dependency was defined as the use of 2 or more units of red blood cell products during the 8 weeks prior to a study visit. New onset of transfusion independency was defined as the use of 0 or 1 unit of red blood cell products during the 8 weeks prior to a study visit. Full analysis set was used for analysis.

Full analysis set (FAS): The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline (BL), end of treatment (up to 28 days post last treatment) (EOT)

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Percentage of Participants				
number (not applicable)				
From independency at BL to independency at EOT	0			
From dependency at BL to independency at EOT	2.1			
From missing at BL to independency at EOT	0			
From independency at BL to dependency at EOT	0			
From dependency at BL to dependency at EOT	10.4			

From missing at BL to dependency at EOT	35.4			
From independency at BL to missing at EOT	0			
From dependency at BL to missing at EOT	0			
From missing at BL to missing at EOT	52.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of General Practitioner (GP), Specialists' and Urgent Care Visits

End point title	Number of General Practitioner (GP), Specialists' and Urgent Care Visits

End point description:

MRU was assessed according to the number of GP, specialists', and urgent care visits.

Only participants from the full analysis set (FAS), who had evaluable measurements at each timeframe, e.g. from baseline to week 12, were included in the analysis for that timeframe. The FAS included all participants who received at least one administration of study drug and had at least one post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline to week 12, week 12 to, week 24, week 24 to week 36, week 36 to week 48

End point values	Oral INC424 at a dose of 15 or 20 mg twice daily			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Visits				
median (full range (min-max))				
GP visits baseline to week 12 (n 45)	0 (0 to 4)			
GP visits week 12 to week 24 (n 36)	0 (0 to 1)			
GP visits week 24 to week 36 (n 33)	0 (0 to 2)			
GP visits week 36 to week 48 (n 33)	0 (0 to 3)			
Specialists visits baseline to week 12 (n 47)	0 (0 to 8)			
Specialists visits week 12 to week 24 (n 36)	0 (0 to 2)			
Specialists visits week 24 to week 36 (n 33)	0 (0 to 4)			
Specialists visits week 36 to week 48 (n 33)	0 (0 to 3)			
Urgent care visits baseline to week 12 (n 48)	0 (0 to 1)			
Urgent care visits week 12 to week 24 (n 39)	0 (0 to 0)			

Urgent care visits week 24 to week 36 (n 33)	0 (0 to 1)			
Urgent care visits week 36 to week 48 (n 33)	0 (0 to 1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ruxolitinib

Reporting group description:

Ruxolitinib

Serious adverse events	Ruxolitinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 48 (47.92%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hernia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Disorientation				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysarthria			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Migraine			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIIth nerve paralysis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Splenomegaly			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Cataract				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eyelid ptosis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Dysphagia				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Skin lesion				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal impairment				

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Kidney infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Staphylococcal sepsis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ruxolitinib		
Total subjects affected by non-serious adverse events subjects affected / exposed	47 / 48 (97.92%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Weight increased			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	8		
Contusion			
subjects affected / exposed	11 / 48 (22.92%)		
occurrences (all)	13		
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 48 (18.75%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	11 / 48 (22.92%)		
occurrences (all)	11		
Paraesthesia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Lethargy			

subjects affected / exposed occurrences (all)	10 / 48 (20.83%) 10		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 20 / 48 (41.67%) 33 3 / 48 (6.25%) 4 17 / 48 (35.42%) 26		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 11 / 48 (22.92%) 13 5 / 48 (10.42%) 5		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Mouth ulceration	 3 / 48 (6.25%) 3 11 / 48 (22.92%) 14 3 / 48 (6.25%) 3 4 / 48 (8.33%) 6 7 / 48 (14.58%) 11		

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	4 / 48 (8.33%) 4 11 / 48 (22.92%) 16 3 / 48 (6.25%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all)	 5 / 48 (10.42%) 6 6 / 48 (12.50%) 7 12 / 48 (25.00%) 27		
Skin and subcutaneous tissue disorders Night sweats subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 6 / 48 (12.50%) 7 3 / 48 (6.25%) 3 3 / 48 (6.25%) 3 5 / 48 (10.42%) 7		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	 3 / 48 (6.25%) 3		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	7		
Flank pain			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Muscle spasms			
subjects affected / exposed	7 / 48 (14.58%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Lower respiratory tract infection			
subjects affected / exposed	7 / 48 (14.58%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2012	Amendment 1 was issued prior to recruitment of the first patient, introduced the following changes: The primary endpoint was amended to incorporate a composite endpoint (i.e. reduction in spleen size and or reduction in total symptom scores).
02 August 2012	Amendment 2 was issued after the inclusion of approximately 50% of patients and introduced changes: The number of patients included in the trial was increased from 33 to 45 patients to allow more patients. The sample size calculation was updated to reflect the increased number of patients that would be analyzed in the trial.
24 June 2013	Amendment 3 was issued after the inclusion of 100% of patients and introduced the following changes: Since the first patient was enrolled into the study, the understanding of ruxolitinib in the treatment of MPNs had changed and thus revisions of the protocol were necessary to adapt these new findings. An interim analysis was also added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported