Clinical trial results:
Polycythemia Vera Symptom Study Evaluating Ruxolitinib Versus Hydroxyurea in a Randomized, Multicenter, Double-Blind, Double-Dummy, Phase 3 Efficacy and Safety Study of Patient Reported Outcomes

Summary

EudraCT number	2012-002318-37
Trial protocol	GB BE IT ES IE
Global end of trial date	24 June 2016

Results information

Result version number	v1 (current)
This version publication date	21 July 2017
First version publication date	21 July 2017

Trial information

Trial identification

Sponsor protocol code	INCB18424-357

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01632904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cut-Off, Wilmington, United States, 19803
Public contact	Incyte Corporation Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.com
Scientific contact	Incyte Corporation Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.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	27 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2014
Global end of trial reached?	Yes
Global end of trial date	24 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the RELIEF study was to compare symptoms in polycythemia vera (PV) subjects treated with ruxolitinib versus subjects treated with hydroxyurea (HU) as measured by the percent of subjects who achieved a clinically meaningful symptom improvement (ie, total symptom score reduction of ≥ 50% reduction) at Week 16 compared to Baseline. The study was also designed to demonstrate that these responses are durable with continued treatment.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 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 States: 56
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 18
Worldwide total number of subjects	110
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)	51
From 65 to 84 years	57
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 54 study centers including 1 in Belgium, 6 in Germany, 3 in Italy, 3 in Spain, 4 in UK (total 17 ex-US), and 37 in United States.

Pre-assignment

Screening details:

Subjects with polycythemia vera (PV) who received hydroxyurea (HU) for at least 12 weeks and had been receiving a stable dose for 4 weeks before screening and still had symptoms related to PV were enrolled. Subjects were randomized (1:1) to 1 of 2 treatment groups:
• Ruxolitinib and HU-placebo
• HU and ruxolitinib-placebo

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ruxolitinib

Arm description:

Ruxolitinib will be orally self-administered at a starting dose of 10 mg (two 5 mg tablets) twice a day. Dose increases of 5 mg (1 tablet) in twice-daily increments are permitted after 4 weeks and again after 8 weeks of therapy for subjects who meet prespecified criteria for inadequate efficacy.
HU-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose. When adjustments are made to the ruxolitinib dose, the dose of HU-placebo will be adjusted concurrently.

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

Dosage and administration details:

Ruxolitinib will be orally self-administered at a starting dose of 10 mg (two 5 mg tablets) twice a day. Dose increases of 5 mg (1 tablet) in twice-daily increments are permitted after 4 weeks and again after 8 weeks of therapy for subjects who meet prespecified criteria for inadequate efficacy.

Investigational medicinal product name	HU-placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

All placebo will be self-administered, and dosing will be the same as with the blinded dose. When adjustments are made to the ruxolitinib dose, the dose of HU-placebo will be adjusted concurrently.

Arm title	Hydroxyurea

Arm description:

Hydroxyurea (HU) (500 mg capsules) will be orally self-administered at the dose that the subject was receiving previously. The dose may be increased after 4 weeks and again after 8 weeks of therapy to optimize efficacy for subjects meeting prespecified criteria.

Ruxolitinib-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose.
When adjustments are made to the HU dose, the dose of ruxolitinib-placebo will be adjusted concurrently.

Arm type	Active comparator
Investigational medicinal product name	Hydroxyurea (HU)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Hydroxyurea (500 mg capsules) will be orally self-administered at the dose that the subject was receiving previously. The dose may be increased after 4 weeks and again after 8 weeks of therapy to optimize efficacy for subjects meeting prespecified criteria.

Investigational medicinal product name	Ruxolitinib-placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

All placebo will be self-administered, and dosing will be the same as with the blinded dose.
When adjustments are made to the HU dose, the dose of ruxolitinib-placebo will be adjusted concurrently.

Number of subjects in period 1	Ruxolitinib	Hydroxyurea
Started	54	56
Completed	47	50
Not completed	7	6
Physician decision	-	1
Adverse event, non-fatal	4	1
Subject decision	3	2
Reason for discontinuation not available	-	1
Disease Progression	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Ruxolitinib
Reporting group description:	
Ruxolitinib will be orally self-administered at a starting dose of 10 mg (two 5 mg tablets) twice a day. Dose increases of 5 mg (1 tablet) in twice-daily increments are permitted after 4 weeks and again after 8 weeks of therapy for subjects who meet prespecified criteria for inadequate efficacy. HU-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose. When adjustments are made to the ruxolitinib dose, the dose of HU-placebo will be adjusted concurrently.	
Reporting group title	Hydroxyurea
Reporting group description:	
Hydroxyurea (HU) (500 mg capsules) will be orally self-administered at the dose that the subject was receiving previously. The dose may be increased after 4 weeks and again after 8 weeks of therapy to optimize efficacy for subjects meeting prespecified criteria. Ruxolitinib-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose. When adjustments are made to the HU dose, the dose of ruxolitinib-placebo will be adjusted concurrently.	

Reporting group values	Ruxolitinib	Hydroxyurea	Total
Number of subjects	54	56	110
Age categorical Units: Subjects			
Adults (18-64 years)	28	23	51
From 65-84 years	25	32	57
85 years and over	1	1	2
Age continuous Units: years			
arithmetic mean	63.1	64.2	
standard deviation	± 11.68	± 12.68	-
Gender categorical Units: Subjects			
Female	30	22	52
Male	24	34	58

End points

End points reporting groups

Reporting group title	Ruxolitinib

Reporting group description:

Ruxolitinib will be orally self-administered at a starting dose of 10 mg (two 5 mg tablets) twice a day. Dose increases of 5 mg (1 tablet) in twice-daily increments are permitted after 4 weeks and again after 8 weeks of therapy for subjects who meet prespecified criteria for inadequate efficacy.
HU-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose.
When adjustments are made to the ruxolitinib dose, the dose of HU-placebo will be adjusted concurrently.

Reporting group title	Hydroxyurea

Reporting group description:

Hydroxyurea (HU) (500 mg capsules) will be orally self-administered at the dose that the subject was receiving previously. The dose may be increased after 4 weeks and again after 8 weeks of therapy to optimize efficacy for subjects meeting prespecified criteria.
Ruxolitinib-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose.
When adjustments are made to the HU dose, the dose of ruxolitinib-placebo will be adjusted concurrently.

Primary: Percentage of Subjects Achieving a ≥ 50% Improvement From Baseline in Total Symptom Score-Cytokine (TSS-C) at Week 16, as Measured by the Modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Diary

End point title	Percentage of Subjects Achieving a ≥ 50% Improvement From Baseline in Total Symptom Score-Cytokine (TSS-C) at Week 16, as Measured by the Modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Diary

End point description:

Symptoms of polycythemia vera were assessed using a modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) electronic diary. Using the diary, patients rated the following symptoms on a scale from 0 (absent) to 10 (worst imaginable): tiredness, itching, muscle aches, night sweats, and sweats while awake. The total symptom score ranged from 0-50 and was calculated as the sum of the 5 symptom scores. A higher score indicates worse symptoms.
For the overall TSS-C score, only those subjects with a baseline score of 0 and a Week 16 score of 0 or missing were excluded from the analysis.

End point type	Primary

End point timeframe:

From Baseline to Week 16

End point values	Ruxolitinib	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[1]	54[2]		
Units: Percentage of participants				
number (not applicable)	43.4	29.6		

Notes:

[1] - Intent-to-Treat (ITT); all subjects randomized in the study.

[2] - Intent-to-Treat (ITT); all subjects randomized in the study.

Statistical analyses

Statistical analysis title	Improvement From Baseline in TSS-C
Comparison groups	Ruxolitinib v Hydroxyurea
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.139
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	4.04

Secondary: Percentage of Subjects Achieving ≥ 50% Improvement From Baseline in the Individual Symptom Scores for TSS-C at Week 16

End point title	Percentage of Subjects Achieving ≥ 50% Improvement From Baseline in the Individual Symptom Scores for TSS-C at Week 16

End point description:

The TSS-C cluster includes tiredness, itching, muscle aches, night sweats, and sweats while awake.

For individual symptom scores within the TSS-C cluster, only those subjects with a baseline score of 0 and a Week 16 score of 0 or missing were excluded from the analysis.

End point type	Secondary

End point timeframe:

From Baseline to Week 16

End point values	Ruxolitinib	Hydroxyurea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[3]	54[4]		
Units: Percentage of participants				
number (not applicable)				
Tiredness (n= 50, 53)	40	26.4		
Itching (n= 48, 50)	54.2	32		
Muscle aches (n= 47, 49)	38.3	30.6		
Night sweats (n= 42, 48)	47.6	41.7		
Sweats while awake (n= 42, 46)	54.8	34.8		

Notes:

[3] - Intent-to-Treat (ITT); all subjects randomized in the study.

[4] - Intent-to-Treat (ITT); all subjects randomized in the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The duration of the study up to Week 16. This time frame defines the blinded, comparative phase of the study where the majority of patients remained on their original randomized assignment and exposure between ruxolitinib and hydroxyurea was similar.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Ruxolitinib

Reporting group description:

Ruxolitinib will be orally self-administered at a starting dose of 10 mg (two 5 mg tablets) twice a day. Dose increases of 5 mg (1 tablet) in twice-daily increments are permitted after 4 weeks and again after 8 weeks of therapy for subjects who meet prespecified criteria for inadequate efficacy.
HU-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose.
When adjustments are made to the ruxolitinib dose, the dose of HU-placebo will be adjusted concurrently.

Reporting group title	Hydroxyurea

Reporting group description:

Hydroxyurea (HU) (500 mg capsules) will be orally self-administered at the dose that the subject was receiving previously. The dose may be increased after 4 weeks and again after 8 weeks of therapy to optimize efficacy for subjects meeting prespecified criteria.
Ruxolitinib-placebo All placebo will be self-administered, and dosing will be the same as with the blinded dose.
When adjustments are made to the HU dose, the dose of ruxolitinib-placebo will be adjusted concurrently.

Serious adverse events	Ruxolitinib	Hydroxyurea	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 54 (9.26%)	4 / 56 (7.14%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hemoglobin decreased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	1 / 54 (1.85%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 54 (1.85%)	0 / 56 (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			
Cerebral ischemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 56 (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			
Chest discomfort			
subjects affected / exposed	1 / 54 (1.85%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spondylolisthesis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 56 (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			
Hyperkalemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Ruxolitinib	Hydroxyurea	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 54 (92.59%)	45 / 56 (80.36%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 54 (3.70%)	4 / 56 (7.14%)	
occurrences (all)	2	4	
Hypotension			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 54 (5.56%)	3 / 56 (5.36%)	
occurrences (all)	3	3	
Chest pain			

subjects affected / exposed	2 / 54 (3.70%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	3 / 54 (5.56%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Fatigue			
subjects affected / exposed	11 / 54 (20.37%)	6 / 56 (10.71%)	
occurrences (all)	12	7	
Pyrexia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 56 (1.79%)	
occurrences (all)	2	2	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 54 (3.70%)	2 / 56 (3.57%)	
occurrences (all)	3	2	
Dyspnoea			
subjects affected / exposed	3 / 54 (5.56%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Epistaxis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 56 (3.57%)	
occurrences (all)	1	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 54 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	5	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 54 (1.85%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Disturbance in attention			
subjects affected / exposed	2 / 54 (3.70%)	1 / 56 (1.79%)	
occurrences (all)	2	1	
Insomnia			

subjects affected / exposed	4 / 54 (7.41%)	2 / 56 (3.57%)	
occurrences (all)	4	4	
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 54 (3.70%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Platelet count decreased			
subjects affected / exposed	0 / 54 (0.00%)	3 / 56 (5.36%)	
occurrences (all)	0	5	
Weight decreased			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Weight increased			
subjects affected / exposed	3 / 54 (5.56%)	0 / 56 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 54 (5.56%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Palpitations			
subjects affected / exposed	2 / 54 (3.70%)	1 / 56 (1.79%)	
occurrences (all)	2	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 54 (12.96%)	5 / 56 (8.93%)	
occurrences (all)	8	6	
Headache			
subjects affected / exposed	9 / 54 (16.67%)	3 / 56 (5.36%)	
occurrences (all)	11	4	

Paraesthesia			
subjects affected / exposed	2 / 54 (3.70%)	2 / 56 (3.57%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	8 / 54 (14.81%)	5 / 56 (8.93%)	
occurrences (all)	11	6	
Leukopenia			
subjects affected / exposed	1 / 54 (1.85%)	2 / 56 (3.57%)	
occurrences (all)	1	6	
Lymphadenopathy			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	1 / 54 (1.85%)	3 / 56 (5.36%)	
occurrences (all)	1	5	
Thrombocytopenia			
subjects affected / exposed	2 / 54 (3.70%)	5 / 56 (8.93%)	
occurrences (all)	2	6	
Thrombocytosis			
subjects affected / exposed	2 / 54 (3.70%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	2 / 54 (3.70%)	1 / 56 (1.79%)	
occurrences (all)	2	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	3 / 54 (5.56%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 54 (5.56%)	2 / 56 (3.57%)	
occurrences (all)	3	2	
Abdominal pain			
subjects affected / exposed	3 / 54 (5.56%)	3 / 56 (5.36%)	
occurrences (all)	4	3	

Abdominal pain upper			
subjects affected / exposed	3 / 54 (5.56%)	0 / 56 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	4 / 54 (7.41%)	7 / 56 (12.50%)	
occurrences (all)	4	8	
Diarrhoea			
subjects affected / exposed	5 / 54 (9.26%)	11 / 56 (19.64%)	
occurrences (all)	5	17	
Dry mouth			
subjects affected / exposed	2 / 54 (3.70%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	6 / 54 (11.11%)	3 / 56 (5.36%)	
occurrences (all)	6	5	
Stomatitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 56 (3.57%)	
occurrences (all)	1	3	
Vomiting			
subjects affected / exposed	2 / 54 (3.70%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 54 (5.56%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Erythema			
subjects affected / exposed	1 / 54 (1.85%)	2 / 56 (3.57%)	
occurrences (all)	1	4	
Hyperhidrosis			
subjects affected / exposed	4 / 54 (7.41%)	2 / 56 (3.57%)	
occurrences (all)	4	3	
Night sweats			
subjects affected / exposed	3 / 54 (5.56%)	1 / 56 (1.79%)	
occurrences (all)	3	1	
Pruritus			

subjects affected / exposed	6 / 54 (11.11%)	6 / 56 (10.71%)	
occurrences (all)	11	10	
Rash			
subjects affected / exposed	6 / 54 (11.11%)	0 / 56 (0.00%)	
occurrences (all)	7	0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 54 (3.70%)	3 / 56 (5.36%)	
occurrences (all)	2	3	
Back pain			
subjects affected / exposed	1 / 54 (1.85%)	4 / 56 (7.14%)	
occurrences (all)	1	4	
Muscle spasms			
subjects affected / exposed	4 / 54 (7.41%)	3 / 56 (5.36%)	
occurrences (all)	5	3	
Myalgia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 56 (1.79%)	
occurrences (all)	2	2	
Neck pain			
subjects affected / exposed	2 / 54 (3.70%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 56 (3.57%)	
occurrences (all)	1	3	
Nasopharyngitis			
subjects affected / exposed	1 / 54 (1.85%)	2 / 56 (3.57%)	
occurrences (all)	2	2	
Upper respiratory tract infection			
subjects affected / exposed	3 / 54 (5.56%)	2 / 56 (3.57%)	
occurrences (all)	4	2	
Urinary tract infection			

subjects affected / exposed	4 / 54 (7.41%)	1 / 56 (1.79%)	
occurrences (all)	4	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 54 (1.85%)	3 / 56 (5.36%)	
occurrences (all)	1	3	
Hyperkalaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 56 (1.79%)	
occurrences (all)	0	2	
Hyperuricaemia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2012	Amendment 1 was issued before the Protocol was submitted to sites or health authorities and before any subjects had received study drug. This was the first version of the Protocol released for subject participation.
01 July 2013	The primary purpose of the amendment was the following: • Include additional exploratory objectives and endpoints to evaluate Hct control, complete hematologic remission, and palpable spleen length in the study population. • Revise prior phlebotomy inclusion criteria for those subjects with splenomegaly. • Provide specific requirements for study discontinuation for disease progression. • Provide more explicit guidelines for laboratory assessment frequency in the case of dose titrations or temporary interruptions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27858987