



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 \geq 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ Improvement From Baseline in the Individual Symptom Scores for TSS-C at Week 16

| | |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Achieving $\geq 50\%$ 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

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

| | | | |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 | 2 / 56 (3.57%) 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 occurrences (all) | 2 / 54 (3.70%) 2 | 2 / 56 (3.57%) 4 | |
| Blood and lymphatic system disorders | | | |
| Anemia subjects affected / exposed occurrences (all) | 8 / 54 (14.81%) 11 | 5 / 56 (8.93%) 6 | |
| Leukopenia subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 2 / 56 (3.57%) 6 | |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 54 (0.00%) 0 | 2 / 56 (3.57%) 2 | |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 54 (1.85%) 1 | 3 / 56 (5.36%) 5 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 5 / 56 (8.93%) 6 | |
| Thrombocytosis subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 0 / 56 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Tinnitus subjects affected / exposed occurrences (all) | 2 / 54 (3.70%) 2 | 1 / 56 (1.79%) 1 | |
| Eye disorders | | | |
| Vision blurred subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | 0 / 56 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 3 | 2 / 56 (3.57%) 2 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 54 (5.56%) 4 | 3 / 56 (5.36%) 3 | |

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

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

| | | | |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 54 (7.41%) 4 | 1 / 56 (1.79%) 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: <ul style="list-style-type: none">• 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>