



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/ μ L 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/ μ L (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/ μ L and platelet count had never been below 150,000/ μ L at a prior laboratory evaluation while receiving ruxolitinib.
- ANC levels had remained at or above 1000/ μ L 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 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 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.

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|----------------|---------|
| 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.

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|----------------|-----------|
| 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.

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|---|-----------|
| 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

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|-----------------|---|
| 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

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|---|-----------|
| 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

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|-----------------|----------------------------|
| 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.

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| End point type | Secondary |
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End point timeframe:

week 12, week 24, week 26, week 48

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|--------------------------------------|--|--|--|--|
| 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 (\pm 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

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|-----------------|---|
| End point title | Percentage of Participants With Transfusion Dependency Status |
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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.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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|--|--|--|--|--|
| 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

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|-----------------|--|
| 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.

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|----------------|-----------|
| 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

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

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|-----------------------|-------------|
| 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 occurrences (all) | 4 / 48 (8.33%) 4 | | |
| Weight increased subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 4 | | |
| Injury, poisoning and procedural complications | | | |
| Fall subjects affected / exposed occurrences (all) | 6 / 48 (12.50%) 8 | | |
| Contusion subjects affected / exposed occurrences (all) | 11 / 48 (22.92%) 13 | | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 9 / 48 (18.75%) 9 | | |
| Headache subjects affected / exposed occurrences (all) | 11 / 48 (22.92%) 11 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 3 / 48 (6.25%) 3 | | |
| Lethargy | | | |

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

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

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