## Sponsor

Novartis Pharmaceuticals

## Generic Drug Name

Ruxolitinib

## Trial Indication(s)

Primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF)

## Protocol Number

CINC424A2352

## Protocol Title

A Randomized Study of INC424 (INCB018424) Tablets Compared to Best Available Therapy in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera-Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis

## Clinical Trial Phase

Phase 3

## Phase of Drug Development

Phase III

## Study Start/End Dates

Study Start Date: 1 July 2009 (Actual)
Primary Completion Date: 4 Jan 2011 (Actual)

Study Completion Date: 4 March 2015 (Actual)

## Reason for Termination (If applicable)

## Study Design/Methodology

This was an open-label, randomized study comparing the efficacy and safety of ruxolitinib phosphate tablets (INC424) versus the best available Investigator-selected therapy in myelofibrosis (MF) patients with splenomegaly of at least 5 cm below the costal margin by manual palpation and either 2 (intermediate risk) or 3 or more (high risk) prognostic factors (Cervantes et al, 2009). The starting dose of ruxolitinib was determined based on the baseline platelet count; the maximum dose on study did not exceed 25 mg twice daily (bid). Patients were stratified at baseline by prognostic category of intermediate−2 (2 risk factors) or high (3 or more risk factors) risk according to:

- Age > 65 years
- Presence of constitutional symptoms (weight loss, fever, night sweats)
- Marked anemia (hemoglobin < 10g/dL)
- Leukocytosis (history of white blood cell counts > 25 x 109/L)
- Circulating blasts ≥ 1%

## Centers

63 centers in 10 countries: Sweden(2), Netherlands(6), Italy(6), United Kingdom(4), France(17), Spain(3), Germany(9), Switzerland(1), Belgium(10), Austria(5)

## Objectives:

Primary Objective
The primary objective of Study A2352 was to compare the efficacy, safety, and tolerability of ruxolitinib given twice daily compared to BAT, in patients with PMF, PPV-MF or PET-MF.

Secondary Objectives
The secondary objective of Study A2352 was to evaluate the population pharmacokinetics (PK) of ruxolitinib:

- Duration of maintenance of a ≥ 35% reduction from BL in spleen volume
- Time to achieve a first ≥ 35% reduction in spleen volume from BL
- Progression free survival
- Leukemia free survival
- Overall survival
- Change in bone marrow histomorphology

## Test Product (s), Dose(s), and Mode(s) of Administration

Ruxolitinib was the investigational treatment in this study. Five milligram tablets were administered orally without regard to food in an outpatient setting in accordance with the specified dosing schedule

## Statistical Methods

**Efficacy**:

DoMSR was defined as an interval between the first spleen volume measurement with ≥ 35%reduction from baseline, and the first scan that was no longer equal to a 35% reduction and that was a >25% increase over nadir. DoMSR was evaluated using the Kaplan−Meier estimate for each treatment arm.

PFS was defined as the interval between randomization and earliest of either increase in spleen volume ≥ 25% from on−study nadir, splenic irradiation, splenectomy, leukemia, or death.

LFS was defined as the interval between randomization and the earliest date of either (1) the bone marrow blast count of 20% or greater; (2) the date of the first peripheral blast count of 20% or greater that was subsequently confirmed to have been sustained for at least 8 weeks; (3) the date of death from any cause.

Since the analysis at 144 weeks showed that the majority of LFS events were deaths, a new sensitivity analysis has been introduced to evaluate the transformation to leukemia. Time to leukemic transformation has been defined as the interval between randomization and the date of bone marrow blast count of 20% or greater OR the date of the first peripheral blast count of 20% or greater that is subsequently confirmed to have been sustained for at least 8 weeks.

OS was defined as the interval between randomization and date of death from any cause.

PFS, LFS, time to leukemic transformation, and OS were summarized using Kaplan−Meier estimates for each treatment arm. The estimates were supplemented by tables of number of events and probability estimates at several timepoints. The summary of first events of PFS, LFS and time to leukemic transformation was tabulated by treatment arm. Hazard ratio and 95% confidence intervals were estimated using the Cox proportional hazards model stratified by baseline prognostic category assigned at randomization. P−values for stratified 2−sided log−rank test were provided at face value without adjustment for multiple comparisons.

Bone marrow histomorphology was tabulated by fibrosis grade at baseline and post−baseline. Descriptive statistics (i.e., number of patients and patient percentages) were used.

**Safety:**

Safety data were summarized by means of reported AEs, clinically notable adverse events, and hematology laboratory abnormalities. AEs and laboratory abnormalities were presented for five groups of patients: (1) ruxolitinib randomized phase, (2) ruxolitinib randomized + extension phase, (3) BAT randomized phase, (4) BAT after crossover to ruxolitinib, and (5) all ruxolitinib treated patients. Safety events in group 1 are included in group 2; safety events in groups 2 and 4 are included in group 5.

Following categories of AEs during treatment or within 28 days after stopping treatment were summarized by treatment group: general AEs of all grade and grade 3/4, deaths, SAEs, AEs requiring study discontinuation, and AEs of special interest.

AEs of special interest included thrombocytopenia, erythropenia, leukopenia, hemorrhage, malignancies, urinary tract infections, herpes zoster infections, tuberculosis, dizziness, bruising events and weight gain. These grouped terms were defined by standard/Novartis MedDRA which group one or more MedDRA preferred terms that relate to a defined medical condition or area of interest in order to aid in case identification. Laboratory data were classified into Common Toxicity Criteria (CTC) grades according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (NCI−CTCAE), Version 3.0. A severity grade of 0 was assigned when the value was within normal limits. In the case when a local laboratory normal range overlapped into the higher

(i.e., non−zero) CTC grade or was recorded with a wrong original unit, the laboratory value was still taken as within normal limits and assigned a CTC grade of zero. Hematology parameters were summarized with shift tables and by incidence of new or worsened abnormalities

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Subjects must be diagnosed with PMF, PPV-MF or PET-MF according to the 2008 World Health Organization criteria
- Subjects with MF requiring therapy must be classified as high risk OR intermediate risk level 2 according to the prognostic factors defined by the International Working Group
- Subjects with an ECOG performance status of 0, 1, 2 or 3
- Subjects with peripheral blood blast count of < 10%.
- Subjects who have not previously received treatment with a JAK inhibitor

Exclusion Criteria:
- Subjects with a life expectancy of less than 6 months
- Subjects with inadequate bone marrow reserve as demonstrated by specific clinical laboratory counts
- Subjects with any history of platelet counts < 50,000/µL or ANC < 500/µL except during treatment for a myeloproliferative disorder or treatment with cytotoxic therapy for any other reason
- Subjects with inadequate liver or renal function
- Subjects with clinically significant bacterial, fungal, parasitic or viral infection which require therapy
- Subjects with an active malignancy over the previous 5 years except specific skin cancers
- Subjects with severe cardiac conditions
- Subjects who have had splenic irradiation within 12 months

## Participant Flow Table

### Primary Endpoint Analysis (Interim)

| | Ruxolitinib | Best Available Therapy (BAT) | Rux after cross-over from BAT |
|---|---|---|---|
| **Started** | 146 | 73 | 0[1] |

| | | | |
|---|---|---|---|
| **Completed** | 91[2] | 31[3] | 0 |
| **Not Completed** | 55[2] | 42[3] | 0 |
| Adverse Event | 12 | 4 | 0 |
| Withdrawal by Subject | 2 | 9 | 0 |
| Protocol Violation | 2 | 0 | 0 |
| Disease Progression | 1 | 3 | 0 |
| Non-compliance with study Medication | 2 | 0 | 0 |
| Non-compliance with study procedures | 0 | 1 | 0 |
| Other Reasons | 7 | 7 | 0 |
| Entered Extension phase INC424 | 29 | 18 | 0 |

[1] No cross-overs for this portion of study
[2] Participants ongoing in the randomized treatment phase for INC424/INCB018424 group
[3] Participants ongoing in the randomized treatment phase for the BAT group

## Overall Disposition at 5 year follow-up

| | Ruxolitinib | Best Available Therapy (BAT) | Rux after cross-over from BAT |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Started** | 146 | 28 | 45 |
| **Crossed over after qualifying event** | 0 | 0 | 27 |
| **Crossed over after AMEND 5** | 0 | 0 | 12 |
| **Crossed over: Other** | 0 | 0 | 6 |
| **Completed** | 39 | 0 | 11 |
| **Not Completed** | 107 | 28 | 34 |
| Adverse Event | 35 | 5 | 10 |
| Withdrawal by Subject | 10 | 9 | 0 |
| Protocol Violation | 2 | 0 | 5 |
| Disease Progression | 32 | 4 | 7 |
| Non-compliance with study medication | 4 | 0 | 1 |
| Non-compliance with study procedures | 0 | 1 | 0 |
| Lack of Efficacy | 8 | 0 | 5 |
| Including stem cell transplantation | 16 | 9 | 6 |

## Baseline Characteristics

| | Ruxolitinib | Best Available Therapy (BAT) | Total |
|---|---|---|---|
| **Number of Participants [units: participants]** | 146 | 73 | 219 |
| **Age Continuous** (units: years) Mean ± Standard Deviation | 65.1±9.74 | 65.2±10.27 | 65.2±9.89 |
| **Gender, Male/Female** (units: participants) | | | |
| Female | 63 | 31 | 94 |
| Male | 83 | 42 | 125 |
| **Disease Profile - Type of Myelofibrosis (MF)**[1] (units: Participants) | | | |
| Primary Myelofibrosis | 77 | 39 | 116 |
| Post-polycythemia vera-myelofibrosis | 48 | 20 | 68 |
| Post-essential thrombocythemia-myelofibrosis | 21 | 14 | 35 |

[1] Disease characteristics at baseline. Overall, (primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis(PPV-MF) and post-essential thrombocythemia-myelofibrosis (PET-MF) were diagnose in participants. The frequency of PMF was similar between ruxolitinib and BAT arms. In addition, the frequencies of PPV-MF and PET-MF were also similar between both treatment arms.

## Summary of Efficacy

The clinical benefit of ruxolitinib treatment demonstrated in the efficacy analysis at Week 48 (primary analysis CSR) was maintained with continued exposure to ruxolitinib in the longer term as shown by the analyses of time-to event endpoints (DoMSR, PFS, LFS and OS). Comparisons to BAT are difficult to make as the results in the BAT arm are most likely driven by a large number of patients who were allowed to cross over and receive ruxolitinib following the implementation of Amendment 5:

- The probability of maintaining spleen volume reduction at the 3.0-year time point was 0.51 (95% CI: 0.38, 0.62), and was 0.48 (95% CI: 0.35, 0.60) for later time points up to 5.0 years (not applicable for BAT);
- The risk of leukemia or death was reduced by ruxolitinib by 29% (HR=0.71; 95%CI: 0.47, 1.08. The Kaplan-Meier estimate of LFS at the 5.0-year time point was 0.54 for the ruxolitinib arm (95%CI: 0.45, 0.62), and was 0.44 (95% CI: 0.31, 0.56) for BAT;
- The risk of progression or death was reduced by ruxolitinib by 22% (HR=0.78; 95% CI: 0.53, 1.16).
- The risk of progression or death was reduced by ruxolitinib by 22% (HR=0.78; 95% CI: 0.53, 1.16). The Kaplan-Meier estimate of PFS at the 5.0-year time point was 0.24 (95% CI: 0.16, 0.32) for the ruxolitinib arm, and was 0.18 (95% CI: 0.07, 0.33) for BAT;
- The risk of death was reduced by 33% in the ruxolitinib arm compared to the BAT arm (HR=0.67; 95%CI: 0.44, 1.02). The Kaplan-Meier estimate of OS at the 5.0-year time point was 0.56 (95%CI: 0.47, 0.64) for the ruxolitinib arm, and was 0.44 (95%CI: 0.31, 0.56) for BAT

## Primary Outcome Result(s)

**Percentage of participants with at least 35% reduction in spleen volume from baseline at week 48**

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 144 | 72 |
| **Percentage of participants with at least 35% reduction in spleen volume from baseline at** | 28.5 | 0 |

**week 48**
(units: Percentage of Participants)

## Secondary Outcome Result(s)

### Duration of maintenance of spleen volume reduction (Medians)

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 78 | 1 |
| **Duration of maintenance of spleen volume reduction (Medians)** (units: years) Median (95% Confidence Interval) | 3.22 (1.65 to N/A)[1] | N/A (N/A to N/A)[2] |

[1] Upper limit not available
[2] There was only one BAT patient responder (≥ 35% reduction in spleen volume) but no consecutive readings to determine any value for duration of response - no Median or CI possible to calculate

### Duration of maintenance of spleen volume reduction (Kaplan-Meier estimates)

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 78 | 1 |
| **Duration of maintenance of spleen volume reduction** | | |

**(Kaplan-Meier estimates)**
(units: KM estimate of probability)
Number (95% Confidence Interval)

| | | |
|---|---|---|
| 1.0 year | 0.72 (.60 to .81) | N/A (N/A to N/A)[1] |
| 1.5 years | 0.67 (0.55 to 0.77) | N/A (N/A to N/A)[1] |
| 2.0 years | 0.63 (0.50 to 0.73) | N/A (N/A to N/A)[1] |
| 2.5 years | 0.54 (0.41 to 0.65) | N/A (N/A to N/A)[1] |
| 3.0 years | 0.51 (0.38 to 0.62) | N/A (N/A to N/A)[1] |
| 3.5 years | 0.48 (0.35 to 0.60) | N/A (N/A to N/A)[1] |
| 4.0 years | 0.48 (0.35 to 0.60) | N/A (N/A to N/A)[1] |
| 4.5 years | 0.48 (0.35 to 0.60) | N/A (N/A to N/A)[1] |
| 5.0 years | 0.48 (0.35 to 0.60) | N/A (N/A to N/A)[1] |

[1] There was only one BAT patient responder (≥ 35% reduction in spleen volume) but no consecutive readings to determine any value for duration of response - no Median or CI possible to calculate

## Percentage of participants with at least 35% reduction in spleen volume from baseline at week 24

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 144 | 72 |
| **Percentage of participants with at least** | 31.9 | 0 |

**35% reduction in spleen volume from baseline at week 24**
(units: Percentage of Participants)

## Time to first at least 35% reduction in spleen volume from baseline by treatment (Primary analysis)

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 69 | 1 |
| **Time to first at least 35% reduction in spleen volume from baseline by treatment (Primary analysis)** (units: weeks) Number (95% Confidence Interval) | | |
| 12 weeks | 0.23 (0.14 to 0.34) | 0 (NA to NA)[1] |
| 24 weeks | 0.67 (0.54 to 0.76) | 1 (NA to NA)[1] |
| 36 weeks | 0.87 (0.76 to 0.93) | 1 (NA to NA)[1] |
| 48 weeks | 0.97 (0.89 to 0.99) | 1 (NA to NA)[1] |

[1] There was only one BAT patient responder (≥ 35% reduction in spleen volume) but no consecutive readings to determine any value for duration of response - no Median or CI possible to calculate

## Progression-free survival (PFS)

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|

| | | |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 146 | 73 |
| **Progression-free survival (PFS)** (units: years) Median (95% Confidence Interval) | 1.6 (1.2 to 2.3) | 1.4 (1.1 to 1.9) |

## Leukemia-free survival (LFS)

| | **Ruxolitinib** | **Best Available Therapy (BAT)** |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 146 | 73 |
| **Leukemia-free survival (LFS)** (units: Years) Median (95% Confidence Interval) | NA (NA to NA)[1] | 4.1 (2.4 to NA)[2] |

[1] Median was not reached
[2] Upper limit was not estimable

## Overall survival (OS)

| | **Ruxolitinib** | **Best Available Therapy (BAT)** |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 146 | 73 |
| **Overall survival (OS)** (units: Years) Median (95% Confidence | NA (NA to NA)[1] | 4.1 (2.4 to NA)[2] |

Interval)

[1] Median was not reached
[2] Upper limit of CI was not estimable

## Percentage of participants with bone marrow histomorphology at week 48(primary analysis)

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 146 | 73 |
| **Percentage of participants with bone marrow histomorphology at week 48(primary analysis)** (units: Percentage of participants) | | |
| Grade 0 | 2.7 | 0.0 |
| Grade 1 | 7.5 | 2.7 |
| Grade 2 | 8.9 | 6.8 |
| Grade 3 | 24.0 | 15.1 |
| Missing Grade | 56.8 | 75.3 |

## Bone marrow histomorphology

| | Ruxolitinib - Grade 0 | Ruxolitinib - Grade 1 | Ruxolitinib - Grade 2 | Ruxolitinib - Grade 3 | Ruxolitinib - Missing | Best Available Therapy (BAT) - Grade 0 | Best Available Therapy (BAT) - Grade 1 | Best Available Therapy (BAT) - Grade 2 | Best Available Therapy (BAT) - Grade 3 | Best Available Therapy - Missing |
|---|---|---|---|---|---|---|---|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 146 | 146 | 146 | 146 | 146 | 73 | 73 | 73 | 73 | 73 |

**Bone marrow histomorphology**
(units: Number of patients)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Postbaseline Grade 0 | 1 | 1 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 0 |
| Postbaseline Grade 1 | 0 | 10 | 9 | 2 | 0 | 0 | 1 | 0 | 1 | 0 |
| Postbaseline Grade 2 | 0 | 2 | 8 | 8 | 1 | 0 | 0 | 4 | 1 | 0 |
| Postbaseline Grade 3 | 0 | 6 | 19 | 28 | 2 | 0 | 0 | 4 | 8 | 3 |
| Postbaseline Missing | 2 | 2 | 17 | 20 | 3 | 2 | 2 | 19 | 24 | 4 |

## Duration of follow-up by treatment

| | Ruxolitinib | Best Available Therapy (BAT) |
|---|---|---|
| **Number of Participants Analyzed [units: participants]** | 146 | 73 |
| **Duration of follow-up by treatment** (units: Number of Participants) | | |
| <=1 year | 16 | 15 |
| >1 year - <=2 years | 21 | 10 |
| >2 years - <=3 years | 9 | 13 |
| >3 years - <=4 years | 12 | 5 |
| >4 years - <=5 years | 27 | 8 |
| 5 years | 61 | 22 |

## Summary of Safety

## Safety Results

### Serious Adverse Events by System Organ Class

| | |
|---|---|
| **Source Vocabulary for Table Default** | MedDRA 17.1 |
| **Assessment Type for Table Default** | Systematic Assessment |

| | Ruxolitinib Randomized N = 146 | Ruxolitinib Randomized + Extension Phase N = 146 | BAT Randomized N = 73 | Ruxolitinib cross-over N = 45 |
|---|---|---|---|---|
| **Total participants affected** | 51 (34.93%) | 85 (58.22%) | 22 (30.14%) | 20 (44.44%) |
| **Blood and lymphatic system disorders** | | | | |
| Anaemia | 8 (5.48%) | 10 (6.85%) | 4 (5.48%) | 2 (4.44%) |
| Anaemia of chronic disease | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Coagulopathy | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Febrile neutropenia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Leukocytosis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Lymphadenopathy | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Neutropenia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |

| | | | | |
|---|---|---|---|---|
| Pancytopenia | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Paratracheal lymphadenopathy | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Splenic infarction | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Splenomegaly | 0 (0.00%) | 2 (1.37%) | 1 (1.37%) | 1 (2.22%) |
| Thrombocytopenia | 1 (0.68%) | 2 (1.37%) | 1 (1.37%) | 4 (8.89%) |
| Thrombotic microangiopathy | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Cardiac disorders** | | | | |
| Acute coronary syndrome | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Aortic valve stenosis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Arteriosclerosis coronary artery | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Atrial fibrillation | 1 (0.68%) | 4 (2.74%) | 1 (1.37%) | 0 (0.00%) |
| Atrial flutter | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Atrioventricular block | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Bradycardia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Cardiac arrest | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Cardiac failure | 3 (2.05%) | 5 (3.42%) | 1 (1.37%) | 1 (2.22%) |
| Cardiopulmonary failure | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Congestive cardiomyopathy | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Coronary artery stenosis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Hypertensive heart disease | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Ischaemic cardiomyopathy | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |

| | | | | |
|---|---|---|---|---|
| Myocardial infarction | 0 (0.00%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Right ventricular failure | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Sick sinus syndrome | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Stress cardiomyopathy | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Supraventricular tachycardia | 0 (0.00%) | 3 (2.05%) | 1 (1.37%) | 0 (0.00%) |
| **Ear and labyrinth disorders** | | | | |
| Vertigo | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| **Eye disorders** | | | | |
| Keratitis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Ocular vascular disorder | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Visual impairment | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Gastrointestinal disorders** | | | | |
| Abdominal pain | 3 (2.05%) | 6 (4.11%) | 2 (2.74%) | 1 (2.22%) |
| Abdominal pain upper | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 1 (2.22%) |
| Abdominal wall haematoma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Anal fistula | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Ascites | 0 (0.00%) | 1 (0.68%) | 2 (2.74%) | 0 (0.00%) |
| Colitis ischaemic | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Constipation | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Diarrhoea | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Enteritis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Enterocolitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Faeces discoloured | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |

| | | | | |
|---|---|---|---|---|
| Gastric varices | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Gastritis haemorrhagic | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Gastrointestinal haemorrhage | 1 (0.68%) | 1 (0.68%) | 1 (1.37%) | 1 (2.22%) |
| Gastrointestinal ulcer | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Haematemesis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 1 (2.22%) |
| Haematochezia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Haemorrhoids | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Ileus paralytic | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Incarcerated umbilical hernia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Inguinal hernia | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Intestinal perforation | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Oesophageal haemorrhage | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Oesophageal varices haemorrhage | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pancreatitis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Peritoneal haemorrhage | 0 (0.00%) | 0 (0.00%) | 2 (2.74%) | 0 (0.00%) |
| Rectal haemorrhage | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Retroperitoneal haemorrhage | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Small intestinal perforation | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Subileus | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Umbilical hernia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Upper gastrointestinal haemorrhage | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 1 (2.22%) |
| Varices oesophageal | 3 (2.05%) | 4 (2.74%) | 0 (0.00%) | 1 (2.22%) |

| | | | | |
|---|---|---|---|---|
| **General disorders and administration site conditions** | | | | |
| Asthenia | 1 (0.68%) | 1 (0.68%) | 1 (1.37%) | 0 (0.00%) |
| Chest pain | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Disease progression | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| General physical health deterioration | 2 (1.37%) | 4 (2.74%) | 1 (1.37%) | 0 (0.00%) |
| Generalised oedema | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Inflammation | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Multi-organ failure | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 1 (2.22%) |
| Oedema peripheral | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 1 (2.22%) |
| Performance status decreased | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pyrexia | 4 (2.74%) | 5 (3.42%) | 1 (1.37%) | 1 (2.22%) |
| **Hepatobiliary disorders** | | | | |
| Cholecystitis | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Cholelithiasis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Hepatic failure | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Hepatomegaly | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Portal hypertension | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Portal vein thrombosis | 1 (0.68%) | 2 (1.37%) | 1 (1.37%) | 0 (0.00%) |
| **Infections and infestations** | | | | |
| Bronchitis | 3 (2.05%) | 4 (2.74%) | 1 (1.37%) | 0 (0.00%) |
| Bronchopneumonia | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Campylobacter infection | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |

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| Cellulitis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 1 (2.22%) |
| Clostridium difficile colitis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Clostridium difficile infection | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Cystitis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Endocarditis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Enterococcal sepsis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Escherichia infection | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Escherichia urinary tract infection | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 2 (4.44%) |
| Febrile infection | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Gastroenteritis | 2 (1.37%) | 3 (2.05%) | 0 (0.00%) | 0 (0.00%) |
| Gastroenteritis clostridial | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Gastroenteritis norovirus | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Gastrointestinal infection | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Genital infection female | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Herpes zoster | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Infection | 0 (0.00%) | 3 (2.05%) | 0 (0.00%) | 1 (2.22%) |
| Influenza | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Klebsiella sepsis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Lung infection | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Meningitis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Meningoencephalitis herpetic | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Neutropenic sepsis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Oesophageal infection | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Peritonitis | 0 (0.00%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |

| | | | | |
|---|---|---|---|---|
| Pneumocystis jirovecii pneumonia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pneumonia | 2 (1.37%) | 11 (7.53%) | 4 (5.48%) | 1 (2.22%) |
| Pneumonia mycoplasmal | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Postoperative abscess | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pseudomonal sepsis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pyelonephritis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Respiratory tract infection | 2 (1.37%) | 3 (2.05%) | 0 (0.00%) | 0 (0.00%) |
| Sepsis | 0 (0.00%) | 2 (1.37%) | 0 (0.00%) | 1 (2.22%) |
| Sepsis syndrome | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Septic shock | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 1 (2.22%) |
| Skin infection | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Soft tissue infection | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Staphylococcal infection | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Staphylococcal sepsis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Testicular abscess | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Tuberculosis | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Urinary tract infection | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 1 (2.22%) |
| Urinary tract infection bacterial | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Urosepsis | 1 (0.68%) | 3 (2.05%) | 0 (0.00%) | 0 (0.00%) |
| Viral infection | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Injury, poisoning and procedural complications** | | | | |
| Concussion | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |

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| Ear injury | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Femoral neck fracture | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Femur fracture | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Head injury | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Hip fracture | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Injury | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Lumbar vertebral fracture | 0 (0.00%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Post procedural haemorrhage | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Postoperative fever | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Postoperative respiratory distress | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Post-traumatic pain | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Procedural pain | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Radius fracture | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Seroma | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Thoracic vertebral fracture | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Traumatic fracture | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Traumatic haematoma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Traumatic intracranial haemorrhage | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| **Investigations** | | | | |
| Alanine aminotransferase increased | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Blood creatinine increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |

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| C-reactive protein increased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Gamma-glutamyltransferase increased | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Haemoglobin decreased | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Weight increased | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Metabolism and nutrition disorders** | | | | |
| Fluid retention | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Hyperkalaemia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Hyperuricaemia | 0 (0.00%) | 3 (2.05%) | 0 (0.00%) | 0 (0.00%) |
| Hyponatraemia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Arthralgia | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Back pain | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 1 (2.22%) |
| Bone pain | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Groin pain | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Intervertebral disc protrusion | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Osteitis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Osteolysis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Osteonecrosis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | |
| Acute myeloid | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |

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| leukaemia | | | | |
| Basal cell carcinoma | 1 (0.68%) | 4 (2.74%) | 0 (0.00%) | 0 (0.00%) |
| Bowen's disease | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Bronchial carcinoma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Carcinoma in situ | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Cholesteatoma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Gastric cancer | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Glioblastoma multiforme | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Lung adenocarcinoma recurrent | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Lung neoplasm malignant | 0 (0.00%) | 1 (0.68%) | 1 (1.37%) | 0 (0.00%) |
| Malignant melanoma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Metastases to lymph nodes | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Metastases to peritoneum | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Metastases to spine | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Metastatic squamous cell carcinoma | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Myelofibrosis | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Neuroendocrine carcinoma metastatic | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Prostate cancer | 1 (0.68%) | 4 (2.74%) | 0 (0.00%) | 0 (0.00%) |
| Squamous cell carcinoma of skin | 3 (2.05%) | 5 (3.42%) | 1 (1.37%) | 0 (0.00%) |
| **Nervous system disorders** | | | | |
| Aphasia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |

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|---|---|---|---|---|
| Cerebral haemorrhage | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 1 (2.22%) |
| Cerebrovascular accident | 1 (0.68%) | 4 (2.74%) | 0 (0.00%) | 0 (0.00%) |
| Coma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Convulsion | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Depressed level of consciousness | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Encephalopathy | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Epilepsy | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Hepatic encephalopathy | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Paraesthesia | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pseudoradicular syndrome | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Somnolence | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Syncope | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Psychiatric disorders** | | | | |
| Abnormal behaviour | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Confusional state | 1 (0.68%) | 3 (2.05%) | 0 (0.00%) | 0 (0.00%) |
| Delusion | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Depression | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Renal and urinary disorders** | | | | |
| Hydronephrosis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Nephrolithiasis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Prerenal failure | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Renal failure | 1 (0.68%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Renal failure acute | 3 (2.05%) | 4 (2.74%) | 1 (1.37%) | 3 (6.67%) |

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| Renal failure chronic | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Renal impairment | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Renal infarct | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Urinary retention | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Reproductive system and breast disorders** | | | | |
| Benign prostatic hyperplasia | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Uterine prolapse | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Acute respiratory failure | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Cough | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Dyspnoea | 2 (1.37%) | 4 (2.74%) | 3 (4.11%) | 0 (0.00%) |
| Interstitial lung disease | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Lung disorder | 0 (0.00%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Lung infiltration | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pleural effusion | 1 (0.68%) | 1 (0.68%) | 1 (1.37%) | 1 (2.22%) |
| Pleurisy | 0 (0.00%) | 2 (1.37%) | 0 (0.00%) | 0 (0.00%) |
| Pneumonitis | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Productive cough | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pulmonary embolism | 1 (0.68%) | 4 (2.74%) | 0 (0.00%) | 0 (0.00%) |
| Pulmonary hypertension | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Pulmonary oedema | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 1 (2.22%) |
| Respiratory distress | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Respiratory failure | 0 (0.00%) | 1 (0.68%) | 2 (2.74%) | 0 (0.00%) |
| Tachypnoea | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |

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| **Skin and subcutaneous tissue disorders** | | | | |
| Actinic keratosis | 0 (0.00%) | 0 (0.00%) | 2 (2.74%) | 0 (0.00%) |
| **Vascular disorders** | | | | |
| Aortic aneurysm | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Aortic thrombosis | 0 (0.00%) | 0 (0.00%) | 1 (1.37%) | 0 (0.00%) |
| Arterial stenosis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Circulatory collapse | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Hypertension | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Hypertensive crisis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Intra-abdominal haematoma | 0 (0.00%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |
| Thrombosis | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (2.22%) |
| Venous thrombosis | 1 (0.68%) | 1 (0.68%) | 0 (0.00%) | 0 (0.00%) |

## Other Adverse Events by System Organ Class

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| **Source Vocabulary for Table Default** | MedDRA 17.1 |
| **Assessment Type for Table Default** | Systematic Assessment |
| **Frequent Event Reporting Threshold** | 5% |

| | **Ruxolitinib Randomized N = 146** | **Ruxolitinib Randomized + Extension Phase N = 146** | **BAT Randomized N = 73** | **Ruxolitinib cross-over N = 45** |
|---|---|---|---|---|
| **Total participants** | 145 (99.32%) | 145 (99.32%) | 64 (87.67%) | 42 (93.33%) |

| affected | | | | |
|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | |
| Anaemia | 61 (41.78%) | 71 (48.63%) | 8 (10.96%) | 19 (42.22%) |
| Leukocytosis | 7 (4.79%) | 8 (5.48%) | 0 (0.00%) | 2 (4.44%) |
| Thrombocytopenia | 67 (45.89%) | 77 (52.74%) | 10 (13.70%) | 21 (46.67%) |
| **Cardiac disorders** | | | | |
| Angina pectoris | 5 (3.42%) | 8 (5.48%) | 1 (1.37%) | 2 (4.44%) |
| Atrial fibrillation | 2 (1.37%) | 11 (7.53%) | 1 (1.37%) | 1 (2.22%) |
| Palpitations | 8 (5.48%) | 12 (8.22%) | 0 (0.00%) | 2 (4.44%) |
| Tachycardia | 4 (2.74%) | 8 (5.48%) | 4 (5.48%) | 1 (2.22%) |
| **Ear and labyrinth disorders** | | | | |
| Vertigo | 5 (3.42%) | 9 (6.16%) | 1 (1.37%) | 1 (2.22%) |
| **Gastrointestinal disorders** | | | | |
| Abdominal distension | 7 (4.79%) | 11 (7.53%) | 3 (4.11%) | 3 (6.67%) |
| Abdominal pain | 14 (9.59%) | 21 (14.38%) | 12 (16.44%) | 3 (6.67%) |
| Abdominal pain upper | 12 (8.22%) | 16 (10.96%) | 4 (5.48%) | 5 (11.11%) |
| Ascites | 4 (2.74%) | 6 (4.11%) | 3 (4.11%) | 3 (6.67%) |
| Constipation | 12 (8.22%) | 19 (13.01%) | 3 (4.11%) | 2 (4.44%) |
| Diarrhoea | 36 (24.66%) | 55 (37.67%) | 13 (17.81%) | 12 (26.67%) |
| Dyspepsia | 7 (4.79%) | 10 (6.85%) | 4 (5.48%) | 3 (6.67%) |
| Gastrooesophageal reflux disease | 4 (2.74%) | 10 (6.85%) | 0 (0.00%) | 2 (4.44%) |
| Nausea | 21 (14.38%) | 30 (20.55%) | 7 (9.59%) | 5 (11.11%) |
| Vomiting | 16 (10.96%) | 27 (18.49%) | 1 (1.37%) | 4 (8.89%) |

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| **General disorders and administration site conditions** | | | | |
| Asthenia | 28 (19.18%) | 38 (26.03%) | 9 (12.33%) | 10 (22.22%) |
| Chest pain | 0 (0.00%) | 0 (0.00%) | 4 (5.48%) | 4 (8.89%) |
| Chills | 4 (2.74%) | 8 (5.48%) | 0 (0.00%) | 0 (0.00%) |
| Fatigue | 23 (15.75%) | 36 (24.66%) | 8 (10.96%) | 8 (17.78%) |
| General physical health deterioration | 3 (2.05%) | 7 (4.79%) | 4 (5.48%) | 3 (6.67%) |
| Oedema peripheral | 33 (22.60%) | 55 (37.67%) | 21 (28.77%) | 8 (17.78%) |
| Peripheral swelling | 3 (2.05%) | 7 (4.79%) | 0 (0.00%) | 3 (6.67%) |
| Pyrexia | 20 (13.70%) | 36 (24.66%) | 6 (8.22%) | 7 (15.56%) |
| **Infections and infestations** | | | | |
| Bronchitis | 15 (10.27%) | 37 (25.34%) | 5 (6.85%) | 3 (6.67%) |
| Cystitis | 9 (6.16%) | 15 (10.27%) | 3 (4.11%) | 1 (2.22%) |
| Gastroenteritis | 9 (6.16%) | 14 (9.59%) | 1 (1.37%) | 1 (2.22%) |
| Herpes zoster | 9 (6.16%) | 16 (10.96%) | 0 (0.00%) | 5 (11.11%) |
| Lower respiratory tract infection | 2 (1.37%) | 2 (1.37%) | 0 (0.00%) | 3 (6.67%) |
| Nasopharyngitis | 27 (18.49%) | 40 (27.40%) | 9 (12.33%) | 4 (8.89%) |
| Respiratory tract infection | 6 (4.11%) | 9 (6.16%) | 3 (4.11%) | 2 (4.44%) |
| Rhinitis | 7 (4.79%) | 9 (6.16%) | 0 (0.00%) | 1 (2.22%) |
| Upper respiratory tract infection | 6 (4.11%) | 9 (6.16%) | 1 (1.37%) | 2 (4.44%) |
| Urinary tract infection | 11 (7.53%) | 19 (13.01%) | 2 (2.74%) | 6 (13.33%) |
| **Injury, poisoning and procedural complications** | | | | |

| | | | | |
|---|---|---|---|---|
| Fall | 4 (2.74%) | 8 (5.48%) | 1 (1.37%) | 1 (2.22%) |
| **Investigations** | | | | |
| Alanine aminotransferase increased | 2 (1.37%) | 3 (2.05%) | 0 (0.00%) | 3 (6.67%) |
| Aspartate aminotransferase increased | 1 (0.68%) | 3 (2.05%) | 0 (0.00%) | 3 (6.67%) |
| Blood alkaline phosphatase increased | 3 (2.05%) | 3 (2.05%) | 0 (0.00%) | 3 (6.67%) |
| Cardiac murmur | 6 (4.11%) | 8 (5.48%) | 3 (4.11%) | 3 (6.67%) |
| Gamma-glutamyltransferase increased | 7 (4.79%) | 11 (7.53%) | 1 (1.37%) | 1 (2.22%) |
| Haemoglobin decreased | 4 (2.74%) | 6 (4.11%) | 3 (4.11%) | 4 (8.89%) |
| Platelet count decreased | 11 (7.53%) | 12 (8.22%) | 2 (2.74%) | 9 (20.00%) |
| Weight decreased | 3 (2.05%) | 8 (5.48%) | 6 (8.22%) | 2 (4.44%) |
| Weight increased | 23 (15.75%) | 29 (19.86%) | 1 (1.37%) | 5 (11.11%) |
| White blood cell count increased | 3 (2.05%) | 4 (2.74%) | 0 (0.00%) | 4 (8.89%) |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite | 6 (4.11%) | 20 (13.70%) | 4 (5.48%) | 4 (8.89%) |
| Gout | 1 (0.68%) | 6 (4.11%) | 1 (1.37%) | 3 (6.67%) |
| Hyperuricaemia | 1 (0.68%) | 8 (5.48%) | 1 (1.37%) | 0 (0.00%) |
| Iron overload | 2 (1.37%) | 5 (3.42%) | 0 (0.00%) | 3 (6.67%) |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Arthralgia | 19 (13.01%) | 30 (20.55%) | 8 (10.96%) | 7 (15.56%) |

| | | | | |
|---|---|---|---|---|
| Back pain | 18 (12.33%) | 24 (16.44%) | 10 (13.70%) | 3 (6.67%) |
| Bone pain | 9 (6.16%) | 9 (6.16%) | 4 (5.48%) | 2 (4.44%) |
| Muscle spasms | 15 (10.27%) | 28 (19.18%) | 5 (6.85%) | 4 (8.89%) |
| Musculoskeletal chest pain | 4 (2.74%) | 8 (5.48%) | 1 (1.37%) | 3 (6.67%) |
| Musculoskeletal pain | 7 (4.79%) | 11 (7.53%) | 1 (1.37%) | 1 (2.22%) |
| Osteoarthritis | 3 (2.05%) | 9 (6.16%) | 1 (1.37%) | 1 (2.22%) |
| Pain in extremity | 18 (12.33%) | 24 (16.44%) | 4 (5.48%) | 11 (24.44%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | | |
| Basal cell carcinoma | 5 (3.42%) | 11 (7.53%) | 1 (1.37%) | 1 (2.22%) |
| Squamous cell carcinoma of skin | 3 (2.05%) | 10 (6.85%) | 1 (1.37%) | 0 (0.00%) |
| **Nervous system disorders** | | | | |
| Dizziness | 12 (8.22%) | 20 (13.70%) | 5 (6.85%) | 6 (13.33%) |
| Headache | 18 (12.33%) | 23 (15.75%) | 4 (5.48%) | 8 (17.78%) |
| Paraesthesia | 10 (6.85%) | 16 (10.96%) | 4 (5.48%) | 4 (8.89%) |
| Sciatica | 5 (3.42%) | 9 (6.16%) | 1 (1.37%) | 0 (0.00%) |
| **Psychiatric disorders** | | | | |
| Anxiety | 5 (3.42%) | 9 (6.16%) | 0 (0.00%) | 1 (2.22%) |
| Insomnia | 9 (6.16%) | 13 (8.90%) | 7 (9.59%) | 5 (11.11%) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 22 (15.07%) | 38 (26.03%) | 12 (16.44%) | 9 (20.00%) |
| Dyspnoea | 22 (15.07%) | 35 (23.97%) | 13 (17.81%) | 12 (26.67%) |

| | | | | |
|---|---|---|---|---|
| Dyspnoea exertional | 11 (7.53%) | 13 (8.90%) | 2 (2.74%) | 1 (2.22%) |
| Epistaxis | 13 (8.90%) | 18 (12.33%) | 5 (6.85%) | 6 (13.33%) |
| Oropharyngeal pain | 4 (2.74%) | 8 (5.48%) | 3 (4.11%) | 2 (4.44%) |
| Rales | 6 (4.11%) | 8 (5.48%) | 1 (1.37%) | 2 (4.44%) |
| **Skin and subcutaneous tissue disorders** | | | | |
| Ecchymosis | 3 (2.05%) | 8 (5.48%) | 0 (0.00%) | 4 (8.89%) |
| Eczema | 1 (0.68%) | 3 (2.05%) | 4 (5.48%) | 4 (8.89%) |
| Hyperhidrosis | 3 (2.05%) | 11 (7.53%) | 0 (0.00%) | 1 (2.22%) |
| Night sweats | 14 (9.59%) | 27 (18.49%) | 6 (8.22%) | 4 (8.89%) |
| Pruritus | 9 (6.16%) | 17 (11.64%) | 13 (17.81%) | 4 (8.89%) |
| Rash | 8 (5.48%) | 12 (8.22%) | 1 (1.37%) | 2 (4.44%) |
| Rosacea | 2 (1.37%) | 4 (2.74%) | 1 (1.37%) | 3 (6.67%) |
| Skin lesion | 2 (1.37%) | 12 (8.22%) | 0 (0.00%) | 2 (4.44%) |
| **Vascular disorders** | | | | |
| Haematoma | 15 (10.27%) | 22 (15.07%) | 3 (4.11%) | 4 (8.89%) |
| Hypertension | 8 (5.48%) | 19 (13.01%) | 3 (4.11%) | 2 (4.44%) |

## Other Relevant Findings

## Conclusion:

The observations in this final report confirm that ruxolitinib is an effective treatment option for managing disease related splenomegaly and symptoms in patients with myelofibrosis. The short term benefits that are apparent with ruxolitinib are maintained with continued treatment over longer periods of time with an acceptable and manageable tolerability profile. There is also a distinct survival advantage that is apparent with ruxolitinib in the study despite a majority of the patients in the BAT comparator arm crossing over to receive ruxolitinib following the primary analysis. In conclusion, these data

continue to demonstrate that with longer treatment and follow up, ruxolitinib has a favorable efficacy and safety profile. Taken together with the evidence of improved survival, these findings further demonstrate that ruxolitinib has a positive benefit−risk ratio and thus represents a valuable therapeutic option for patients with MF.

## Date of Clinical Trial Report

Primary completion: 17 Oct 2011

Final report: 17 Aug 2015