22 January 2015
EMA/139813/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Jakavi

International non-proprietary name: RUXOLITINIB

Procedure No. EMEA/H/C/002464/II/0016

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine transaminase
AML	Acute myeloid leukemia
AST	Aspartate transaminase
AUC	Area under the curve
AUC	Area under the concentration-time curve
BAT	Best available therapy
Bid	twice a day
CHR	Complete hematological remission
CL/F	Clearance
Cmax	Maximum plasma concentration
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
EC	European Commission
ELN	European Leukemia Net
ET	Essential thrombocythemia
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastro-intestinal
HCT	Hematocrit
HU	Hydroxyurea
INC424B	Ruxolitinib, Jakiva, Jakifa
JAK	Janus kinase
LPFT	Last patient first tretment
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NMSC	Non-melanoma skin cancer
od	Once daily

peg-IFNα	Pegylated interferon alpha
PET-MF	Post essential thrombocytopenia myelofibrosis
PK	Pharmacokinetics
PMF	Primary myelofibrosis
Pop PK	Population PK
PPV-MF	Post-polycythemia vera-myelofibrosis
PR	Partial response
PT	Preferred term
PV	Polycythemia vera
QoL	Quality of life
SAE	Serious adverse event
SAF	Symptom assessment form
SEM	Standard error of mean
sNDA	Supplemental new drug application
SOC	System organ class
SPA	Special protocol assessment
STAT	Signal transducers and activators of transcription
T1/2	Half-life
Tmax	Time needed to reach maximum concentration of drug in plasma
TSS	Total symptom score
TYK2	Tyrosine kinase 2
USA	United States of America
UTI	Urinary tract infection
WBC	White blood cell
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 10 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name**
Jakavi	RUXOLITINIB

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to add treatment of adult patients with polycythaemia vera resistant to or intolerant of hydroxyurea based on the results of Study B2301 (RESPONSE). As a result, the MAH proposed to update sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. An updated RMP version 4.0 has been provided as part of the application.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/176/2010) on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol Assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Robert James Hemmings

Timetable	Dates
Submission date	10 June 2014
Start of procedure	27 June 2014
CHMP Rapporteur Assessment Report	20 August 2014
CHMP CoRapporteur Assessment Report	18 August 2014
PRAC Rapporteur Assessment Report	25 August 2014
Committees comments on PRAC Rapp Advice	1 September 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	11 September 2014
CHMP comments	15 September 2014
CHMP Rapporteur revised Assessment Report	19 September 2014
Request for supplementary information (RSI) and extension of timetable adopted by the CHMP on	25 September 2014
MAH's responses submitted to the CHMP on	20 November 2014
CHMP Rapporteurs' preliminary joint Assessment Report on the MAH's responses circulated on	23 December 2014
PRAC Rapporteur Assessment Report on the MAH's responses circulated on	23 December 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	09 January 2015
CHMP comments	12 January 2015
CHMP Rapporteurs' updated joint Assessment Report on the MAH's responses circulated on	16 January 2015
Opinion	22 January 2015

2. Scientific discussion

2.1. Introduction

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by clonal expansion of a hematopoietic progenitor, erythrocytosis, often leukocytosis and/or thrombocytosis, and nearly always an activating mutation in Janus kinase 2 (JAK2)(1).

Polycythemia vera is characterized by unregulated production of red cells, white cells, and platelets and complicated by extramedullary hematopoiesis, myelofibrosis, and acute leukemia (2). The increased white blood cell (WBC) and platelet counts results in significantly increased blood viscosity (hyperviscosity), which in turn plays a key role in the development of cardiovascular complications such as myocardial infarct, stroke, transient ischemic attack, deep vein thrombosis and pulmonary embolism.

In a 2006 review of the literature, Johansson and colleagues reported a prevalence of PV of approximately 3.0 cases per 10,000 population (3).

The therapeutic goal for PV patients is to alleviate symptoms, reduce the risk of cardiovascular events and decrease and/or minimize the risk of progression to MF, MDS or acute leukemia(4). In the initial phase of the disease, phlebotomy is the cornerstone of treatment with the objective of maintaining hematocrit values below 45%, a cut-off that has been shown to be associated with a lower risk of cardiovascular death and major thrombosis (5). As PV patients are at a high risk of thrombosis, phlebotomy is often accompanied by low dose aspirin. In a study by the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP), the administration of low dose aspirin was shown to significantly reduce the risk of non-fatal myocardial infarction, non-fatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes when compared to placebo (6).

While phlebotomy and low-dose aspirin are accepted as standard of care for the initial therapy of PV patients, cytoreductive therapy is recommended in patients with persistent hematological abnormalities, clinical symptoms, poor compliance with or intolerance of phlebotomy, and those at a high risk of thrombosis. Most PV patients require cytoreductive therapy during the course of their disease(7).

Hydroxyurea, although not approved in all European countries for the use in the treatment of polycythaemia vera, is often the first-line cytoreductive therapy used in patients with polycythaemia vera (8). However, hydroxyurea-related toxicities often require either drug reduction or drug discontinuation resulting in inadequate management of the disease (9) (10).

The applicant requested the approval for the following indication which has been agreed by the CHMP:

Jakavi is indicated for the treatment of adult patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea" (see SmPC, section 4.1).

The recommended starting dose of Jakavi in polycythaemia vera is 10 mg given orally twice daily. In PV, treatment should also be interrupted when haemoglobin is below 8 g/dl. Dose reductions should also be considered if haemoglobin decreases below 12 g/dl and is recommended if it decreases below 10 g/dl. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. The recommended starting dose for PV patients with ESRD on haemodialysis is a single dose of 10 mg or two doses of 5 mg given 12 hours apart, to be administered post-dialysis and only on the day of haemodialysis (see SmPC section 4.2).

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

Polycythemia vera is estimated to show a mean prevalence of 3.0 in 10'000 in the EU resulting in a market penetration factor (F_{pen}) for ruxolitinib of 0.03%. Using this refined F_{pen}, based on prevalence of the disease, and a maximum daily dose of 50 mg per patient, the predicted environmental concentration (PEC) of ruxolitinib in surface water is 0.0075 µg/L. Adding this value to the PEC previously calculated for the treatment of chronic idiopathic myelofibrosis results in an overall PEC of 0.00786 µg/L, thus remaining below the trigger value for a Phase II assessment.

2.2.2. Discussion and conclusion on non-clinical aspects

In conclusion, it is agreed that the approval of the product for the polycythaemia vera indication will not result in a significant increase in environmental exposure.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study number	Study objectives	Number of patients	Treatment duration	Ruxolitinib dose
Study B2301	PK and exposure-response relationship in patients with polycythemia vera (sparse PK sampling strategy)	N=222 (n=110 ruxolitinib-treated patients)	**Treatment period:** Day 1 to Week 80 **Extension period:** Week 80 to Week 208, only for patients receiving ruxolitinib at Week 80	Starting dose 10 mg bid
Study 256	PK and exposure-response relationship in patients with polycythemia vera (sparse PK sampling strategy)	N=34	Treatment continued until a patient met a withdrawal criterion, had intolerable toxicity or progression of disease, withdrew consent, or the Sponsor terminated the study	Starting doses: 10 mg bid, 25 mg bid, 50 mg qd

bid, twice a day; PK, pharmacokinetics; qd, once daily

2.3.2. Pharmacokinetics

Pharmacokinetic data in the applied indication polycythemia vera (PV) was collected in two studies:

- Study 256 (phase II)
- B2301 (RESPONSE; phase III)

Data from both studies were pooled in a population PK as well as PK/PD analysis.

In addition, the MAH has submitted data from four studies performed in Asian subjects and patients.

- Study A1101 (healthy volunteers, Japan)
- Study A1101 (healthy volunteers, Japan)
- Study A2101 (healthy volunteers, China)
- Study A2202 (myelofibrosis, pan-Asian)

Study 256 was a phase II study with 3 starting dose regimens: 10 mg BID, 25 mg BID and 50 mg QD for 8 weeks (n=6-8/group). In the expansion phase, all patients received 10 mg BID and were allowed to dose adjust. PK venous blood samples were collected on cycle 1 day 15 at pre-dose and 2 and 6 hours after administration of the morning dose. Non-compartmental analysis of the results is shown in Table 1 below.

Table 1. Ruxolibtinib steady state PK parameters from study 256.

Population	Regimen	n	Conc. at 2 h (nM)	Conc. at Pre-dose (nM)	CL/F (L/h)	AUCtau (nM×h)
PV	10 mg bid	19	514±253	96±86	14.3±5.8 13.1	2739±1316 2485
	25 mg bid	7	987±262	297±272	13.7±4.6 13.1	6562±2235 6242
	50 mg qd	6	1661±617	17±15	20.7±6.1 19.9	8534±2728 8197

Values are mean±SD and geometric mean for CL and AUC and mean±SD for concentrations at trough and 2 h post dose.
Source: [Study 256–Table 10]

Study B2301 (RESPONSE) was a randomized, open-labelled phase III study, where patients started on 10 mg BID, and dose-adjustment was allowed with a maximum dose of 25 mg BID. Blood sampling was performed on week 4 (day 28, predose and 0.5, 2 and 4-12 hours), 8, 16 and 32 (pre-dose) and ruzolitinib measured with HPLC/MS/MS. Data were included in a population PK analysis.

A population pharmacokinetics analysis was performed using data from the two studies in PV.

The objectives of the population pharmacokinetic (PK) analysis in the 2 studies were:

- To describe the PK of ruxolitinib in subjects with polycythaemia vera and validate the existing PK model in myelofibrosis using PK data from polycythaemia vera subjects.
- To identify predictors of exposure to the drug (demographics, laboratory values, disease status, concomitant medications) and identify subpopulations with altered PK.
- To estimate the intersubject variability (IIV) of ruxolitinib PK.

The PK sampling strategies are shown in Table 2.

Table 2. Sampling strategies: population pharmacokinetics analysis

Study	PK Sampling Times
INCB 18424-256	Day 15 of Cycle 1: predose, 2 and 6 hours postdose
CINC424B2301	Week 4 in the treatment phase for those randomized to ruxolitinib or Week 4 after initiating INC424 therapy for subjects who randomized to placebo who crossed over to ruxolitinib. In addition, a study visit occurring at least 2 weeks after treatment with a concomitant CYP3A4 inducer was conducted. Sampling timepoints were predose, 0.5 ± 0.25 hours, 2 ± 0.25 hours, and 4 to 12 hours (suggested 5 ± 1 hour) postdose. Weeks 8, 16, and 32: predose

Pharmacokinetic data from the PV population was used as an external validation data set for the existing PK model in MF subjects. Data preparation was performed using SAS v9.2. Exploratory data analyses and presentations of data were performed using S-Plus and SAS. The PK analyses used NONMEM Version 7.1.0.

The existing population PK model for ruxolitinib in MF subjects was a 2 compartment disposition model with first order absorption, absorption lag time (ALAG), and linear elimination. This existing PK model included covariates of gender, which had an effect on CL/F and baseline body weight (BWT), which had an effect on Vc/F. The ruxolitinib data from Studies INCB 18424-256 and RESPONSE were used to validate this existing model. The overall predictive performance of the existing model in MF subjects was evaluated for differences between the measured data and model predictions in terms of bias and precision.

Model-predicted ruxolitinib concentrations were compared with measured concentrations by calculating the population prediction error percent (PE%), the absolute prediction error percent (|PE%|), the individual prediction error percent (IPE%), and the absolute individual prediction error percent (|IPE%|) as described in the Methods section. The mean and median values for the population prediction error percent (PE%) for the observed concentrations in the model validation dataset were 18.4% and 38.5%, respectively. The distribution of PE% suggested that the existing PK model in MF subjects exhibits a moderate under-prediction bias at the population level with more than 75% of PE% > 0. The mean and median values for the absolute prediction error (|PE%|) for the observed concentrations in the model validation dataset are 60.2% and 49.0%, respectively. This indicated that the population model (without interindividual variability effects included) has some degree of imprecision in its estimation of ruxolitinib concentrations in the new data set.

The existing PK model in MF subjects was then applied to pooled data in PV subjects with the re-estimation of some PK parameters. All the parameters in the existing MF model were re-estimated and minimized successfully. However, estimations of IIV in ka and Vp/F were unsuccessful (the variance estimate of the ETA parameter approached 0). The model with no IIV terms in ka and Vp/F was successful, but estimation of Q/F was not robust, with 95% CI including 0. The above models suggest that the PV data may not be sufficient to estimate ka, ALAG1, Q/F, and Vp/F with related IIVs, and hence these parameters with the related IIV terms were fixed to those in MF model. The under-prediction bias was substantially attenuated through the re-estimation of CL/F and Vc/F, IIV in CL/F and Vc/F and residual variability, while keeping the other parameters fixed as in the existing model in MF subjects, and the estimated Vc/F was 64.8 L, which was around 10.6% higher than that in MF PK model, ie, not clinical significant. Furthermore, using the same Vc/F as in the original MF PK model in the model with re-estimated CL/F increased the objective function by 7.2 but decreased the residual variability and IIV in Vc/F by 0.3% and 0.6%, respectively, compared with the previous model. Therefore, the Vc/F estimate

from the original MF model was subsequently used. This model was chosen as the final base model, and its model parameter estimates are presented in Table 3. The magnitude of re-estimated IIV ranged from 26.3 %CV for Vc/F to 42.0 %CV for CL/F. The estimate of residual variability was 34.1 %CV, similar to the magnitude of residual variability estimated in MF subjects.

Table 3. Parameter Estimates and Standard Errors From the Ruxolitinib Final Population Pharmacokinetic Model

	Final Parameter Estimate		Magnitude of Inter-individual Variability (%CV)	
Parameter	Population Mean	%SEM	Final Estimate	%SEM
k_a (h^{-1})	4.12		75.0	
$ALAG_1$ (h)	0.0545		NE	NE
CL/F (L/h)	12.7	3.31	42.0[a]	11.8
V_c/F[b] for subject with body weight of 72.9 kg (L)	58.6		26.3[a]	44.2
V_p/F (L)	11.2		102	
Q/F (L/h)	2.53		NE	NE
RV (%CV)	34.1	8.56	NA	NA
Minimum value of the objective function = 7202.646				

[a] Cov (IIV CL/F, IIV Vc/F) = 0.0716; r = 0.649.

$ALAG_1$ = absorption lag time; CL/F = apparent oral clearance; %CV = percent coefficient of variation; k_a = first-order absorption rate constant; NA = not applicable; NE = not estimated; Q/F = apparent intercompartmental clearance; RV = residual variability; %SEM = percent standard error of the mean; Vp/F = apparent volume of distribution for the tissue (peripheral) compartment.

[b] Vc/F= apparent volume of distribution for the central compartment,

$$V_c / F_j = 58.6 \times \left(\frac{WTKG_j}{72.9} \right)$$, where j represents the jth subject

The covariates that were examined included renal impairment, hepatic impairment, gender, race, ethnicity, age, body weight, study, dose, haematocrit, platelet count, and white blood cell. The concomitant medications explored were CYP3A4 inhibitors. CYP3A4 inducers were not taken by any of the subjects at the time of the PK sampling day, and therefore their effects on PK parameters were not explored. There were only 4 subjects who took weak or other CYP3A4 inhibitors during the PK collection time, and the estimation of effect of CYP3A4 inhibitors was therefore exploratory. The effects of these covariates were evaluated for CL/F only since the other PK parameters were fixed as in the existing PK model in MF subjects.

Baseline haematocrit, platelet count, white blood cell, and haematocrit at each PK visit were specifically investigated as a predictor for CL/F to account for the potential difference in CL/F between the 2 populations. However, none of these covariates were significant predictors for CL/F.

2.3.3. PK/PD modelling

PK-PD analyses were conducted for responder status, spleen volume reduction, absence of phlebotomy eligibility, number of phlebotomies, changes in platelets and haemoglobin. The ruxolitinib exposure measure used in the PK/PD analyses were average daily steady-state plasma concentrations (Css(ave)) expressed in nanomolar (nM) units. A logistic regression was applied to correlate exposure to responder status. A negative binomial regression was applied to correlate exposure to number of phlebotomies. The existing spleen volume, haemoglobin and PLT model in MF patients were validated by the data in PV patients. The MF model used an indirect response model to characterize the time course for spleen volume, with the drug effect characterized via an inhibitory Emax function applied to the zero order formation rate constant for PD response (kin). Semi mechanistic life span models were developed to describe the time course of PLT (blood transfusion independent (BTI) population) and haemoglobin (BTI population); the drug effect in each model was characterized via an inhibitory Emax function applied to the zero-order progenitor cell formation rate constant (kin). The model describing haemoglobin response included a feedback mechanism on kin (which is a function of baseline haemoglobin relative to predicted haemoglobin levels) in order to capture the rebound in haemoglobin concentrations over time in the observed data. In addition, the original population PK/PD models for patients with MF were refined to better describe PD in patients with PV.

Results pop PK

The population PK evaluation in polycythaemia vera patients in the 2 studies showed the following:

- The existing population PK model for ruxolitinib in MF subjects under-predicts the PK in the PV patient population and in particular the oral clearance. The factors contributing to the lower CL/F observed in PV subjects compared to MF subjects are not clear.
- A revised population PK model was developed for PV subjects. The PV model estimated values for particular parameters of primary interest and used other parameters as estimated from the MF model that could not be robustly estimated from the PV data.
- The apparent oral clearance of ruxolitinib is 12.7 L/hr in a typical PV subject with unexplained 42.0 %CV interindividual variability.
- Based on formal covariate analysis, age, gender, and renal dysfunction were not identified as covariates for oral clearance. Though subjects with moderate hepatic impairment seem to have lower CL/F, the subjects with varying degrees of hepatic dysfunction as a group do not show any difference in CL/F compared to subjects with normal hepatic function.
- Given very limited data, influences of the concomitant administration of CYP3A4 inducers and CYP3A4 inhibitors on ruxolitinib PK were not formally assessed, though coadministration of weak or other CYP3A4 inhibitors seemed to lower the clearance of ruxolitinib.
- The CL/F in the Asian group was not significantly different from that in the Caucasian group.
- The apparent central volume of distribution increases linearly with respect to body weight and is 58.6 L for a typical subject weighing 72.9 kg. The remaining unexplained variability in Vc/F is 26.3 %CV.
- The predicted typical value of the terminal elimination half-life using the parameter estimates from the final population model was 4.86 hours in a typical PV subject weighing 72.9 kg.

Results PKPD

In Study B2301, patients with a positive JAK2V617F allele burden at Baseline (classified as JAK2 mutant) treated with ruxolitinib had gradual yet sustained reduction in JAK2V617F allele burden. A mean decline of 12% from baseline was observed at Week 32. The JAK2V617F allele burden in the BAT arm was unchanged through Week 32. With continuous ruxolitinib treatment, a progressive decrease in JAK2V617F allele burden was observed in subsequent measurements reaching a maximal decrease of 35% at the Week 112 visit, the latest timepoint for which data is available. In Study 256, a similar pattern of progressive decrease from Baseline in JAK2V617F allele burden in patients treated with ruxolitinib was observed.

Levels of various cytokines, chemokines and plasma protein markers were evaluated prior to and during treatment in Study B2301. The majority of these analytes were elevated at baseline, which is indicative of the underlying inflammatory component of PV, and is consistent with elevated levels reported in this patient population. In ruxolitinib-randomized patients, several cytokine and plasma protein markers including CRP, CD40, ICAM1, TNFRII and VCAM1 exhibited a decrease or no change in mean percent values from Baseline to Week 32, while the corresponding values in the BAT-randomized patients showed an increase. These results are consistent with the changes in plasma cytokines observed following ruxolitinib treatment in MF patients and are indicative of a reduction in inflammation by ruxolitinib treatment while the BAT group had indications of a worsening inflammatory state.

Exposure-response analyses were conducted for efficacy and safety endpoints. The exposure efficacy analyses were conducted using data only from Study B2301 while exposure-safety analyses included data from both Study B2301 and Study 256. The efficacy parameters evaluated included: change in spleen volume, absence of phlebotomy eligibility, number of phlebotomies and responder status. The exposure-safety analyses evaluated changes in platelets and haemoglobin. The ruxolitinib exposure measures used in the PK/PD analyses were the average daily steady-state plasma concentrations (Css(ave)) expressed in nM. Results from exposure-response analysis for the primary endpoint indicated that Css(ave) was a significant predictor for the responder status at Week 32. The odds of being a responder were increased by 55.5% for every 53.5 nM increase in the average steady state concentration (equivalent to an increase of 5 mg in the total daily dose using typical CL/F value of 12.7 L/h in PV patients). Treatment with ruxolitinib (as opposed to BAT) and Asian race were identified as independent predictors for the absence of phlebotomy eligibility up to 32 weeks (Asians were 4 times more likely to be responders compared to non-Asians). Treatment with ruxolitinib and female gender were identified as significant predictors for number of phlebotomies up to 32 weeks (females had 43% fewer phlebotomies compared to males). The time course of spleen volume change with ruxolitinib treatment indicates that a longer duration is required for PV patients to obtain a maximal effect compared to MF patients. However, PV patients are more sensitive than MF patients to ruxolitinib treatment in that the IC50 for spleen volume reduction in the PV population is less than half that in the MF population. Furthermore, unlike with MF patients, gender was not a significant predictor of the IC50 for spleen volume reduction. Simulations for platelet and haemoglobin changes with dose indicate that at the highest dose of 25 mg bid, platelet counts are maintained at or above 150 × 109/L, starting with a median baseline platelet count of 477× 109/L and haemoglobin concentrations were maintained at or above 104 g/L, starting with a median baseline haemoglobin of 133 g/L.

The IC50 for spleen volume reduction was 75.3 nM in PV subjects, which is lower than that for MF subjects (121.5 nM and 206 nM for female and male, respectively) who are positive for the JAK2V617F mutation, indicating that PV subjects may be more sensitive to ruxolitinib in term of spleen volume reduction.

2.3.4. Discussion on clinical pharmacology

No new information has been generated with regards to absorption, distribution, metabolism, excretion and drug interactions for ruxolitinib in the current application regarding use in PV. PK sampling was performed in the clinical studies in PV, and a new popPK model was developed. The new popPK model suggested about 30% lower mean Cl/F in the PV population, than the Cl/F reported for MF patients. There is however limited data in the PV population, and it is deemed difficult to judge specifics over the difference in pharmacokinetics between the two patient populations and whether it is a real effect of disease on drug kinetics.

The proposed starting dose in PV patients is lower (10 mg bid) compared to a starting dose in MF (15 or 20 mg bid), and each patient is expected to be titrated individually to their own optimal dose based on observed efficacy and safety, and thus no new safety issue is foreseen. In addition, it seems unlikely that the elimination would be qualitatively different to the extent that the current recommendations regarding organ impairment and concomitant medications would not be applicable. Therefore, the recommendations about HI and DDI are also relevant in the PV population (see SmPC section 4.4).

2.3.5. Conclusions on clinical pharmacology

In conclusion, the new PK/PD information provided is considered sufficient.

2.4. Clinical efficacy

2.4.1. Dose response study

In the dose-finding portion of the Phase II Study 256, three different starting doses (10 mg bid, 25 mg bid and 50 mg qd) were tested. These starting doses were chosen based on safety results from a single-dose study in healthy volunteers (Study INCB 18424-131), a multiple dose escalation study in healthy volunteers (Study INCB 18424-132), and a safety and efficacy Phase I/II study in MF patients (Study 251). In Study 256, doses were also allowed to be subsequently modified on an individual basis based on efficacy and safety. A summary of ruxolitinib dose distribution over time in subjects with polycythemia vera in study 256 is presented in table 4.

Table 4. Summary of Ruxolitinib Dose Distribution Over Time in Subjects With Polycythemia Vera (Safety/PV Subjects) Study 256

Treatment Duration	N	Total Daily Dose of Ruxolitinib				
		< 10 mg	10 to 20 mg	> 20 to 30 mg	> 30 to 50 mg	> 50 mg
3 months	34	0	21 (61.8)	1 (2.9)	10 (29.4)	2 (5.9)
6 months	32	0	20 (62.5)	5 (15.6)	4 (12.5)	3 (9.4)
12 months	28	1 (3.6)	17 (60.7)	4 (14.3)	4 (14.3)	2 (7.1)
24 months	25	0	15 (60.0)	4 (16.0)	4 (16.0)	2 (8.0)
36 months	23	0	12 (52.2)	6 (26.1)	4 (17.4)	1 (4.3)
48 months	22	0	13 (59.1)	4 (18.2)	4 (18.2)	1 (4.5)
54 months	6	0	3 (50.0)	2 (33.3)	1 (16.7)	0

Note: Table represents the average total daily dose for each time interval.
Source: Table 14.1.3.2

A summary of subjects with polycythemia vera who achieved a confirmed response at week 8 (itt/pv subjects) in study 256 is presented in Table 5.

Table 5. Summary of Subjects With Polycythemia Vera Who Achieved a Confirmed Response at Week 8 (ITT/PV Subjects) Study 256

	INCB018424 Initial Treatment			
Responders, n (%)	10 mg BID (n = 19)	25 mg BID (n = 8)	50 mg QD (n = 7)	Total (N = 34)
Overall response	11 (58)	4 (50)	4 (57)	19 (56)
Complete response	0	0	0	0
Partial response	11 (58)	4 (50)	4 (57)	19 (56)

Note: Week 8 = Cycle 3 Day 1.
Source: [INCB 18424-256 CSR, Tables 14.1.2.1.2, 14.1.2.2.2, and 14.1.2.2.9]

Numerically the incidence of TEAEs was higher with the higher doses, and lowest with the 10 mg bid dose. More importantly the titration of dose after week 8 showed that majority of patients were kept at the 10 mg bid dose of titrated down from other doses to the 10 mg bid dose, suggesting this was the better tolerated dose. Due to the observed efficacy and safety (i.e., lower incidence of hematological toxicities) associated with a dose of 10 mg bid in PV (the mean and median total daily doses for the entire study were 25.3 mg and 23.2 mg (Study 256), respectively, corresponding to a dose of approximately 10 mg bid), and due to the fact that 65% of PV patients were maintained on doses of 5 or 10 mg bid after 15 months of treatment, 10 mg bid was selected as the starting dose for use in the Phase III Study B2301 in PV.

In the Phase III Study B2301, doses subsequent to the starting dose of 10 mg bid could be adjusted over time based on protocol-defined efficacy and safety criteria so that each patient could individually achieve an optimal dose. Thus, the final dose was likely to be different from the starting dose for many patients. The highest ruxolitinib dose allowed in the study was 25 mg bid. This dose has been established as the maximum tolerated dose (MTD) in healthy volunteers (Study INCB18424-132), and is the maximum recommended dose in the approved indication of MF.

2.4.2. Main study

Study B2301 (RESPONSE)

This study was a randomized, open label, two-arm, multicentre, phase III study comparing the efficacy and safety of ruxolitinib to best available therapy (BAT) in patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea (HU).

Methods

Study participants

Inclusion criteria

The study population included ≥ 18 year-old subjects diagnosed with PV for at least 24 weeks prior to screening and with treatment history for PV that meets the definition of resistance or intolerance to hydroxyurea (HU) by exhibiting at least one of the 5 following criteria:

- HU Resistance (defined after 12 weeks into a course of HU therapy at a dose of at least 2 grams/day or at the subject's maximally tolerated dose if that dose is less than 2 grams/day):
    1. need for phlebotomy to keep hematocrit < 45%, or
    2. platelet count > 400 x 10^9/L and white blood cell count > 10 x 10^9/L, or
    3. failure to reduce splenomegaly extending greater than 10 cm below the costal margin by more than 50%, as measured by palpation;
- HU Intolerance:
    4. Absolute neutrophil count < 1.0 x 10^9/L OR platelet count < 100 x 10^9/L OR hemoglobin < 100 g/L (i.e. 10 g/dL) at the lowest dose of HU required to achieve a response (with response modified from Barosi et al 2009B: hematocrit < 45% without phlebotomy AND/OR all of the following three items: platelet count ≤ 400 x 10^9/L, white blood cell count ≤ 10 x 10^9/L, and non-palpable spleen), or
    5. Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU), defined as CTCAE version 3.0 Grade 3-4, OR more than 1 week of CTCAE version 3.0 Grade

2, OR permanent discontinuation of HU, OR interruption of HU until toxicity resolved, OR hospitalization due to HU toxicity.

To be enrolled, subjects must have required at least 2 phlebotomies within the 24 weeks prior to screening and one phlebotomy within the 16 weeks prior to Screening. The most distant and the most recent phlebotomy within the 24 weeks prior to screening must be at least 4 weeks apart (subjects will be considered to have met this criterion if they have required a phlebotomy within the 16 weeks prior to Screening AND they exhibit a haematocrit > 45% at Screening). The study included subjects with splenomegaly defined as: spleen palpable below the costal margin, provided that MRI (or CT in applicable subjects) spleen assessment during Screening confirms that the spleen is enlarged, defined with a volume of ≥ 450 cm^3, OR spleen non palpable below the costal margin due to body habitus (e.g., in obese subjects), provided that MRI (or CT in applicable subjects) spleen assessment during Screening confirms that the spleen is enlarged, defined with a volume of ≥ 450 cm^3. Subjects at screening must also have reported the following values: ANC ≥ 1.5 x 10^9/L and PLT ≥ 100 x 10^9/L, peripheral blood blast count of 0%, ECOG performance status of 0, 1 or 2. Furthermore, the therapeutic regimen for PV must have been on a stable dose and scheduled for at least 2 weeks prior to screening and no less than 4 weeks prior to randomization (Study Day 1).

The pivotal study conducted in patients with PV who are resistant to or intolerant to hydroxyurea as per the stringent European Leukemia Net (ELN) international working group criteria (Barosi 2009). These criteria, which were developed to provide a basis for selecting patients for studies of new agents in PV, were slightly modified at the time of study design as shown in Table 6.

Table 6. Original ELN and modified HU resistance/intolerance criteria used in Study B2301

Criteria[a]	Original (removal in italic bold)	Modified (additions in bold)
	After 12 weeks of at least 2 grams/day HU the patient shows the following:	After 12 weeks of at least 2 grams/day HU **OR at the patient's maximally tolerated HU dose if that dose is less than 2 grams/day,** the patient shows the following:
1	Need for phlebotomy to keep hematocrit < 45% OR	As original OR
2	Platelets > 400×10^9/L AND WBC > 10×10^9/L OR	As original OR
3	Failure to reduce splenomegaly extending greater than 10 cm below the costal margin by more than 50%, as measured by palpation, ***OR failure to completely relieve symptoms related to splenomegaly*** OR	Failure to reduce splenomegaly extending greater than 10 cm below the costal margin by more than 50%, as measured by palpation, OR
4	Absolute neutrophil count < 1.0×10^9/L OR platelet count < 100×10^9/L OR hemoglobin < 100 g/L at the lowest dose of HU required to achieve a response (response defined as a hematocrit < 45% without phlebotomy AND/OR all of the following three items: platelet count ≤ 400×10^9/L, white blood cell count ≤ 10×10^9/L, and non-palpable spleen) OR	As original, OR
5	Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU)	Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU)**, defined as:** **- CTCAE version 3.0 grade 3-4, OR** **- more than 1 week of CTCAE version 3.0 grade 2, OR** **- permanent discontinuation of HU, OR** **- interruption of HU until toxicity resolved, OR** **- hospitalization due to HU toxicity**

[a]Criteria 1-3 were used to define HU resistance, while criteria 4-5 defined HU intolerance.

Exclusion criteria

Pregnant, lactating or fertile women, unless they were using two birth control methods, were not admitted and active males must use a condom during intercourse while taking the drug and for five half-lives after stopping treatment and should not father a child in this period. Patients were excluded if they had inadequate liver or renal function (as demonstrated by encephalopathy Grade 2 or more per Child-Pugh System, known hepatocellular disease, direct bilirubin ≥ 2 X upper limit of laboratory normal, Alanine aminotransferase > 2.5x ULN, MDRD-eGFR < 30 mL/min/1.73m^2 or on dialysis), gastrointestinal impairment or disease , clinically significant infections or primary immunodeficiency syndromes, active malignancies over the previous 5 years (except treated cervical intraepithelial neoplasia, basal cell carcinoma of the skin, or squamous cell carcinoma of the skin with no evidence for recurrence in the past 3 years), cardiac disease (NYHA Class III or IV), previous history of PEG-IFN-alpha-2a or ^{32}P or JAK inhibitor therapy, current potent systemic CYP3A4 inhibitor (or any investigational agent) treatment.

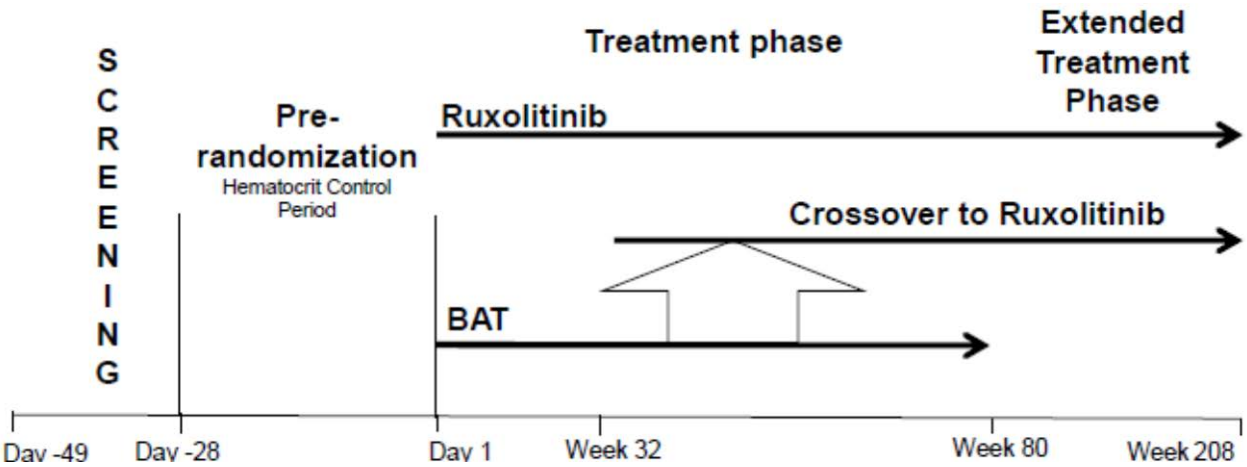
Treatments

Patients were randomized (1:1) to receive either ruxolitinib or best available therapy (BAT). The starting dose of ruxolitinib was 10 mg bid, subsequently adjusted based on safety and efficacy with a maximum dose of 25 mg bid and a minimum of 5 mg per day.

The initial BAT regimen (defined as hydroxyurea, interferon/pegylated interferon, anagrelide, pipobroman, IMIDs or observation), dose and administration schedule could be changed only if specific disease progression criteria or treatment discontinuation criteria were met, based on the judgment of the investigator and in accordance with accepted medical practice.

The study design allowed patients randomized to BAT to crossover to ruxolitinib, as shown in Figure 1, at or after 32 weeks. Crossover from ruxolitinib to BAT was not allowed.

Figure 1. Design of Study B2301



Objectives

The primary objective was to compare the efficacy of ruxolitinib *versus* BAT as assessed by both the absence of phlebotomy eligibility and reduction in spleen volume.

Key secondary objectives included: comparison of the proportion of patients randomized to ruxolitinib *versus* BAT achieving both durable absence of phlebotomy eligibility and durable spleen volume reduction; comparison of the proportion of patients randomized to ruxolitinib *versus* BAT achieving complete haematological remission.

Other secondary objectives included: assessment of the proportion of patients achieving a durable spleen volume reduction; estimation of the proportion of patients achieving a durable complete haematological remission; estimation of the proportion of patients achieving a durable phlebotomy independence; estimation of the duration of both the absence of phlebotomy eligibility and reduction in spleen volume; determination of the overall clinicohaematologic response rate; estimation of the proportion of patients achieving a durable complete or partial clinicohaematologic response; estimation of the duration of the overall clinicohaematologic response; estimation of the proportion of patients achieving both durable absence of phlebotomy eligibility and durable spleen volume reduction 48 weeks after the response was initially documented; evaluation of the safety of ruxolitinib and BAT.

Exploratory objectives included: comparison the proportion of patients achieving white blood cell (WBC) count control to a defined level; comparison of the proportion of patients achieving platelets count control to a defined level; evaluation of changes in Patient-Reported Outcomes (symptoms of PV were captured using the MPN-SAF total symptom score (TSS), an electronic diary completed daily by the patients); evaluation of changes in JAK2V617F allele burden, and evaluation of cytokines and other plasma proteins as potential pharmacodynamic (PD) biomarkers; assessment of the pharmacokinetics of ruxolitinib in PV patients.

Outcomes / endpoints

The primary endpoint was the proportion of subjects achieving a response at Week 32, with response defined as having achieved both of the following: absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32, with no more than one phlebotomy eligibility occurring post-randomization and prior to the Week 8 visit; reduction in spleen volume as assessed by imaging ≥ 35% from baseline at Week 32. Phlebotomy eligibility was defined as a haematocrit greater than 45% and 3% higher than the baseline haematocrit or a haematocrit greater than 48%, whichever is lower.

Key secondary endpoints included:

- Durable primary response defined as achieving the Week 32 primary response endpoint and remaining free from progression 48 weeks after randomisation.

- Complete haematological remission defined as having achieved all of the following: absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32, with no more than one phlebotomy eligibility occurring post-randomization and prior to the Week 8 visit; platelet count ≤ 400 x 109/L at Week 32; wBC count ≤ 10 x 109/L at Week 32.

Other secondary endpoints included:

- Overall (complete or partial) clinicohematologic response defined as achievement of all of the following:

Absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32, with no more than one phlebotomy eligibility occurring post randomization and prior to the Week 8 visit; Spleen volume reduction as assessed by Imaging (see Section 6.2.1) ≥ 35% from baseline at Week 32;Platelet count ≤ 400 x 109/L at Week 32;White blood cell count ≤ 10 x 109/L at Week 32.

Partial clinicohematologic response is defined as achievement of: Absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32, with no more than one phlebotomy eligibility occurring post randomization and prior to the Week 8 visit OR all three of the following: Spleen volume reduction as assessed by Imaging (see Section 6.2.1) ≥ 35% from baseline at Week 32;Platelet count ≤ 400 x 109/L at Week 32;White blood cell count ≤ 10 x 109/L at Week 32.

Explanatory endpoint included:

- Changes in TSS and individual symptom scores from Baseline to Week 32 as measured by the MPN-SAF diary. The electronic MPN-SAF diary was developed to measure, from a patient's perspective, the key symptoms that are important and relevant to the patient's experience with PV. The diary included 14 items representing the following PV-related symptoms: itching, fullness/early satiety, headache, muscle ache, night sweats, sweating while awake, tiredness/fatigue, abdominal discomfort, numbness/tingling in limbs, concentration problems, dizziness, skin redness, vision problem, and ringing in ears. These symptoms have been reported as important and relevant across 3 sources of data: peer-reviewed literature, clinical expert input and by patients themselves. The patients recorded their answers on an 11-point numeric response scale where 0 indicated the absence of a symptom and 10 reflected the worst imaginable symptom intensity.

Total score for cytokine-related symptoms cluster (TSS-C) included cytokine driven symptoms (tiredness/fatigue, itching, muscle aches, night sweats, and sweating while awake).

Total score for hyperviscosity symptom cluster (TSS-H) included symptoms reflecting hyperviscosity and related microvascular changes (vision problems, dizziness, concentration problems, headache, numbness/tingling, ringing in ears, and skin redness).

Total score for splenomegaly symptom cluster (TSS-S) included symptoms related to splenomegaly (abdominal discomfort and fullness/early satiety).

- Changes in EORTC QLQ-C30 score for each of the 5 functional scales, 3 symptom scales, 1 global health status/ quality of life (QoL) scale, and 6 single-item scales from baseline to each visit.

- Changes in individual scores from Baseline as measured by the MPN-SAF questionnaire, MPN-PAF questionnaire and Pruritus Symptom Impact Scale questionnaire.

- The patient's overall sense of whether the treatment was beneficial or not was measured by the Patient Global Impression of Change (PGIC).

Sample size

It was calculated that the study with a total n=200 and 1:1 randomization to treatment arms has 94% power for the test of the primary hypothesis. The type one error was controlled for the primary and key secondary endpoints, at the two sided $\alpha = 0.05$ level. A 30% response rate for patients receiving ruxolitinib and 10% for BAT was assumed. Hydroxyurea stratum specific rates for each treatment arm were obtained assuming that the ratio of HU resistance to HU intolerance is 2:1 and that response rates were 20% higher for patients who were intolerant to HU relative to those who were resistant to HU, i.e. the response rate in HU intolerant patients = 1.2 times the response rate in HU resistant patients.

Randomisation

Patients were randomized (1:1 ratio) to receive either ruxolitinib or BAT treatment. The 2 arms were stratified by HU resistance or HU intolerance.

Blinding (masking)

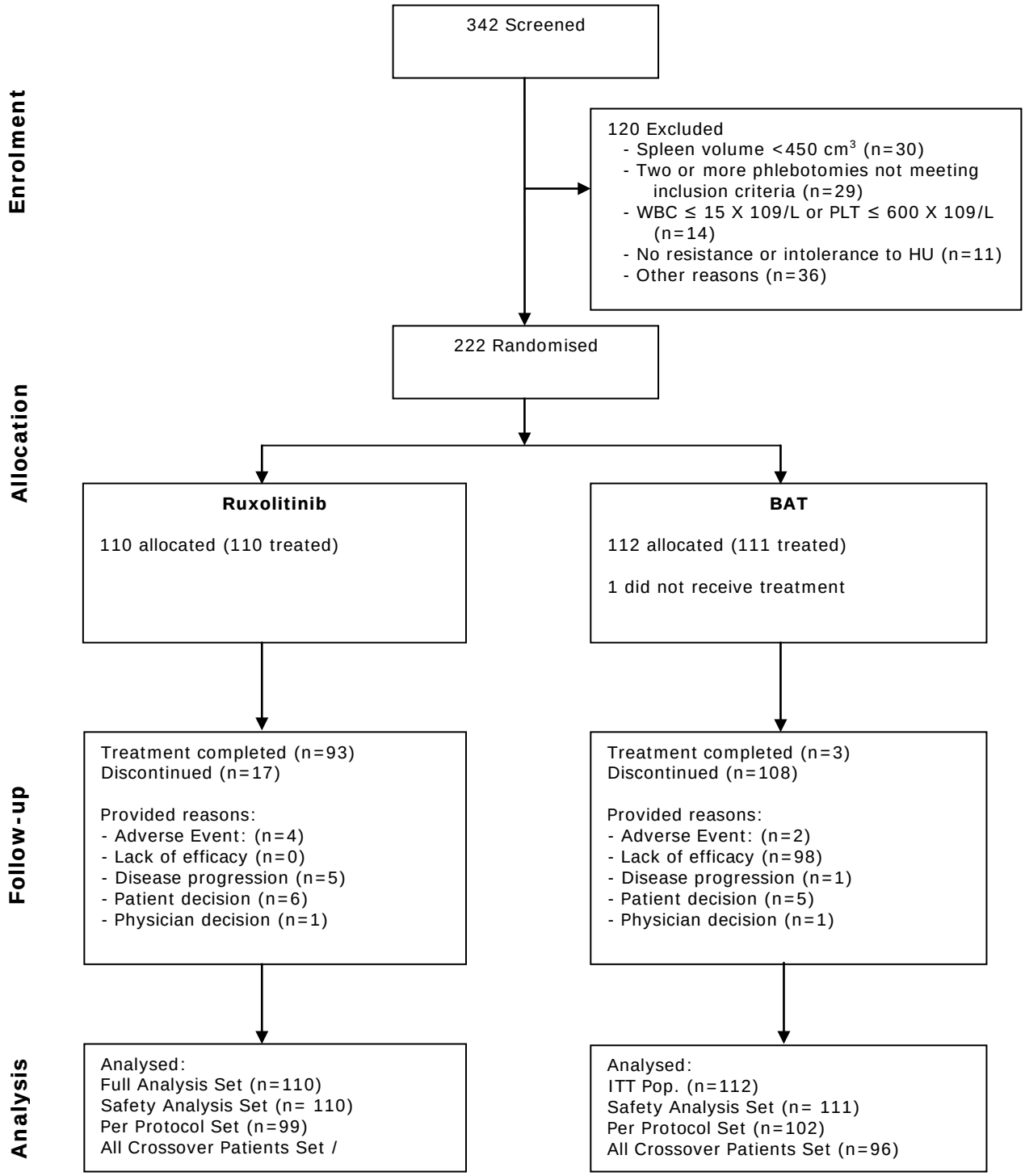
This was an open-label study.

Statistical methods

The null hypotheses for the primary analysis were: H0: $\pi_{INC424} = \pi_{BAT}$ versus H1: $\pi_{INC424} \neq \pi_{BAT}$, where πINC424 and πBAT are the responder rates at Week 32 in the ruxolitinib and BAT group, respectively. Responder rates were presented by treatment group along with 95% confidence intervals using the Clopper Pearson exact method. The Cochran-Mantel-Haenszel (CMH) test stratified by the HU status (HU resistant versus HU intolerant) was applied to compare the two treatment arms. The test was two-sided at the 5% significance level. The overall stratum-adjusted odds ratio was used as a measure of association between treatment and response. The odds ratio was presented with 95% Wald confidence limits. However, if the proportion in any group was less than 4% then the stratified exact CMH test was used. In addition, the adjusted proportion difference and its 95% confidence interval were calculated using CMH weight and Wald-type confidence interval or any other appropriate method. The family wise α-level was controlled at 0.05. Patients with missing assessments that prevented the evaluation of the primary endpoint were considered non-responders.

Results

Participant flow



Recruitment

The first patient was screened on 27 October 2010 and the enrolment was completed on 13 February 2013. A total of 92 centres in 18 countries were involved.

Conduct of the study

The study protocol was amended three times:

Amendment 1 (released 23-Aug-2011, issued after 30 patients had been randomized) revised the inclusion criteria from requiring a palpable spleen length of > 5 cm to requiring palpable splenomegaly confirmed by MRI or CT imaging (volume ≥ 450 cm^3) at screening. Patients with palpable spleen were to be considered eligible if MRI (or CT if applicable) confirmed a spleen volume of ≥ 450 cm^3 (i.e. approximately twice the upper limit of a normal spleen volume). The inclusion criterion that required patients to have a leukocytosis > $15x10^9$/L and/or thrombocytosis > $600x10^9$/L at screening was removed. The definition of unacceptable non-haematological toxicities in HU intolerant patients was extended to include events reflecting severe/very severe toxicities leading to treatment discontinuation or interruption, and hospitalization. The phlebotomy requirement prior to study entry was extended from 12 to 16 weeks between the last phlebotomy and screening, for patients with haematocrit > 45% at screening for the evidence of phlebotomy dependence. The definition of durable response for the primary endpoint and key secondary endpoints was changed to 48 weeks after randomization, however, the definition of duration of primary response was maintained as time from initial response. Bone marrow biopsy was mandated in the event of suspected development of MF or acute leukemia. Sample size was reduced from 300 to 200 patients and the assumption on response rate for durable primary endpoint was modified accordingly.

Table 7. Original ELN and modified HU resistance/intolerance criteria used in Study B2301

Criteria[a]	Original (removal in italic bold)	Modified (additions in bold)
	After 12 weeks of at least 2 grams/day HU the patient shows the following:	After 12 weeks of at least 2 grams/day HU **OR at the patient's maximally tolerated HU dose if that dose is less than 2 grams/day,** the patient shows the following:
1	Need for phlebotomy to keep hematocrit < 45% OR	As original OR
2	Platelets > $400×10^9$/L AND WBC > $10×10^9$/L OR	As original OR
3	Failure to reduce splenomegaly extending greater than 10 cm below the costal margin by more than 50%, as measured by palpation, ***OR failure to completely relieve symptoms related to splenomegaly*** OR	Failure to reduce splenomegaly extending greater than 10 cm below the costal margin by more than 50%, as measured by palpation, OR

Criteria[a]	Original (removal in italic bold)	Modified (additions in bold)
4	Absolute neutrophil count < 1.0×10^9/L OR platelet count < 100×10^9/L OR hemoglobin < 100 g/L at the lowest dose of HU required to achieve a response (response defined as a hematocrit < 45% without phlebotomy AND/OR all of the following three items: platelet count ≤ 400×10^9/L, white blood cell count ≤ 10×10^9/L, and non-palpable spleen) OR	As original, OR
5	Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU)	Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities (such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU)**, defined as:** **- CTCAE version 3.0 grade 3-4, OR** **- more than 1 week of CTCAE version 3.0 grade 2, OR** **- permanent discontinuation of HU, OR** **- interruption of HU until toxicity resolved, OR** **- hospitalization due to HU toxicity**

[a]Criteria 1-3 were used to define HU resistance, while criteria 4-5 defined HU intolerance.

Amendment 2 (released on 13-Apr-2012, issued after 98 patients had been randomized, none of them at the Week 80 visit) extended the treatment period of patients receiving ruxolitinib at Week 80 (end of treatment in the current protocol) by 128 week from Week 80 to Week 208; this period was defined as the Extended Treatment Phase. The PV patients benefitting from ruxolitinib at Week 80 were offered enrolment onto a 128-week Extended Treatment Phase.

Amendment 3 (released on 25-Jun-2013, issued after all patients had been randomized but 6 months prior to database lock for the primary analysis) extended the analysis window for MRI/CT scans from ±7 days to ±28 days. The analysis windows for haematocrit, WBC and platelets were specified in greater detail for individual study visits, and the use of multiple assessments available within an analysis window was defined, in order to minimize missing data, remove any ambiguity and optimize the use of available assessments.

Major protocol deviations are described in Table 8.

Table 8.Table Major Protocol deviations leading to exclusion from per protocol set (FAS - Study B2301)

Protocol deviation	Ruxolitinib N=110 n (%)	BAT N=112 n (%)	All patients N=222 n (%)
Any protocol deviation	11 (10.0)	8 (7.1)	19 (8.6)
Any eligibility criteria deviation	3 (2.7)	3 (2.7)	6 (2.7)
Unconfirmed diagnosis of PV	0	1 (0.9)	1 (0.5)
≥ 2 phlebotomies within the 24 weeks prior to screening and no phlebotomy in the 12 or 16 weeks prior to screening	2 (1.8)	0	2 (0.9)
One phlebotomy due to an elevated hematocrit within the 24 weeks prior to screening and this phlebotomy was more than 13 or 17 weeks prior to screening	0	1 (0.9)	1 (0.5)
No phlebotomy between week 24 and 13 or 17 prior to screening, one phlebotomy due to elevated hematocrit within 13 or 17 weeks of screening and hematocrit at screening ≤ 45%	1 (0.9)	1 (0.9)	2 (0.9)
Any other deviation	9 (8.2)	5 (4.5)	14 (6.3)
Lack of baseline spleen volume within specified window	0	3 (2.7)	3 (1.4)
MRI/CT scan not done within Week 32 efficacy analysis window	2 (1.8)	1 (0.9)	3 (1.4)
Hematocrit not measured within Week 32 efficacy analysis window	2 (1.8)	0	2 (0.9)
Prohibited BAT	0	1 (0.9)[a]	1 (0.5)
Use of medication prohibited in ruxolitinib arm	3 (2.7)[b]	0	3 (1.4)
Use of ruxolitinib in the BAT arm prior to Week 32	1 (0.9)[c]	0	1 (0.5)
Use of combination regimen to treat PV	1 (0.9)	0	1 (0.5)

A patient may have multiple protocol deviations. For the BAT arm the table presents the patients who had a major protocol deviation before crossover.
a. Patient B2301-0603-00002 took busulfan at Day 20 whereas randomized in BAT in observation
b. Two patients randomized to ruxolitinib took anagrelide and one patient had apheresis
c. Patient B2301-0411-00001 was randomized in ruxolitinib arm and had the following deviation: "the patient has taken HU dosing on the same day of the administration ruxolitinib. The patient has taken 10 mg ruxolitinib only as the evening dose". This deviation was coded to "Use of ruxolitinib in the BAT arm prior to Week 32" when the patient was blinded." After unblinding, this deviation was clearly incorrectly categorized. This patient was not a responder; therefore, exclusion from the per-protocol analysis does not change the number of responders in the per protocol analysis.

Baseline data

Baseline demographic and disease characteristics are summarised in Table 9 and Table 10, respectively.

Table 9. Baseline patient characteristics and demographics (Study B2301)

Demographic variable	Ruxolitinib N=110	BAT N=112	All Patients N=222
Age (years)			
Mean (SD)	61.1 (10.48)	59.1 (10.25)	60.1 (10.39)
Median (min–max)	62.0 (34.0-90.0)	60.0 (33.0-84.0)	60.0 (33.0-90.0)
Age category (years) – n (%)			
< 60	49 (44.5)	54 (48.2)	103 (46.4)
≥ 60	61 (55.5)	58 (51.8)	119 (53.6)
Sex – n (%)			
Male	66 (60.0)	80 (71.4)	146 (65.8)
Female	44 (40.0)	32 (28.6)	76 (34.2)
Race – n (%)			
White/Caucasian	98 (89.1)	96 (85.7)	194 (87.4)
Black/African American	1 (0.9)	0	1 (0.5)
Asian	11 (10.0)	16 (14.3)	27 (12.2)
Weight (kg)			
Mean (SD)	76.6 (14.09)	79.0 (17.34)	77.8 (15.83)
Median (min-max)	75.6 (44.5-106.8)	79.0 (44.7-125.5)	77.2 (44.5-125.5)
Height (cm)			
Mean (SD)	172.2 (8.44)	173.3 (9.79)	172.8 (9.14)
Median (min-max)	172.0 (153.0-194.0)	175.0 (149.9-200.7)	173.0 (149.9-200.7)
BMI (kg/m^2)[a]			
Mean (SD)	25.8 (3.82)	26.1 (4.24)	25.9 (4.03)
Median (min-max)	25.3 (16.9-35.2)	25.9 (17.3-38.0)	25.6 (16.9-38.0)
ECOG performance status – n (%)			
0	76 (69.1)	77 (68.8)	153 (68.9)
1	31 (28.2)	34 (30.4)	65 (29.3)
2	3 (2.7)	1 (0.9)	4 (1.8)
3 or 4	0	0	0

a. BMI=mass/height^2. Height was missing at study entry for one patient in the ruxolitinib arm.

Table 10. Disease history at baseline (FAS - Study B2301)

Disease history	Ruxolitinib (N=110)	BAT (N=112)	All Patients (N=222)
Resistance or intolerance to HU[a] – n (%)			
Intolerance	59 (53.6)	61 (54.5)	120 (54.1)
Resistance	51 (46.4)	51 (45.5)	102 (45.9)
Duration of prior HU therapy - week			
Mean (SD)	262.8 (268.34)	244.8 (253.92)	-
Median (min-max)	162.9 (0.1-1088.0)	145.6 (0.1-1088.6)	-
Hematocrit (%)[e]			
Mean (SD)	43.58 (2.196)	43.90 (2.169)	43.74 (2.184)
Median (min-max)	43.30 (39.2-50.5)	44.00 (37.6-50.5)	43.70 (37.6-50.5)
Hematocrit category – n (%)			
< 40	3 (2.7)	4 (3.6)	7 (3.2)
40-45	79 (71.8)	83 (74.1)	162 (73.0)
> 45[e]	28 (25.5)	25 (22.3)	53 (23.9)
Phlebotomies in 24 weeks prior to screening			
1 – n(%)	14 (12.7)	20 (17.9)	34 (15.3)
≥ 2 – n(%)	96 (87.3)	90 (80.4)	186 (83.8)
Missing [3]	0	2 (1.8)	2 (0.9)
Time since diagnosis of PV			
Median (months, range)	98.45 (6.4 - 427.0)	111.65 (6.5 - 271.0)	103.0 (6.4 - 427.0)
JAK2V617 allele burden[d] > 0			
Mean (SD)	76.24 (17.837)	74.97 (22.604)	75.60 (20.356)
Median (min-max)	82.50 (10.0- 96.0)	84.00 (6.0-97.0)	84.00 (6.0-97.0)
JAK2 mutation – n (%)			
Positive	104 (94.5)	107 (95.5)	211 (95.0)
Negative	3 (2.7)	1 (0.9)	4 (1.8)
Missing	3 (2.7)	4 (3.6)	7 (3.2)

a. Resistance or intolerance to HU was reported from IVRS.
b. Not applicable if only one phlebotomy was performed in the time window.
c. Missing if no phlebotomy was performed in the time window.
d. The allele burden is the ratio between mutant and wild type *JAK2* (V617F) in hematopoietic cells. This was only reported for patients who were JAK2 V617F+ at baseline
e. hematocrit baseline value is the last value before randomization. However, to qualify for the study the patients had to have an hematocrit of 40-45% within 14 days prior to randomization (eligibility criterion)

Numbers analysed

The analysis sets for the study are presented in Table 11.

Table 11. Analysis sets (all patients randomized) (Study B2301)

Analysis Set	Ruxolitinib N=110 n (%)	BAT N=112 n (%)	All patients N=222 n (%)
Full Analysis Set (FAS)	110 (100)	112 (100)	222 (100)
Safety Analysis Set (SAS)	110 (100)	111 (99.1)[a]	221 (99.5)
Per-Protocol Set (PPS)[b]	99 (90.0)	102 (91.1)	201 (90.5)
All Crossover Patients Set (ACP)	-	96 (85.7)	-

a. One patient withdrew consent 5 days after randomization in the BAT arm and was not treated.
b. 19 patients had major protocol deviations during the randomized period and 2 patients had major protocol deviations during the crossover period.

The Full Analysis Set (FAS) comprises all patients to whom study treatment had been assigned by randomization.

The Safety Analysis Set (SAS) comprises all patients randomized to the ruxolitinib arm who received at least one dose of study drug and all patients randomized to the BAT who received at least one dose of their intended BAT treatment. Patients randomized to the BAT arm who were intended to receive no therapy were included in the SAS if they completed any post randomization procedures or assessments.

The Per-Protocol Set (PPS) consists of the subset of the patients in the FAS who did not have major protocol deviations at study entry or during the study and who received at least one dose of study drug.

The crossover analysis set (All Crossover Patients, ACP) comprises all patients randomized to and received BAT who received at least one dose of ruxolitinib.

Outcomes and estimation

Primary endpoint: primary response

The efficacy results in terms of primary response at Week 32 are summarised in Table 12, Table 13 and Figure 2.

Table 12. Patients achieving primary response at Week 32 (FAS – Study B2301)

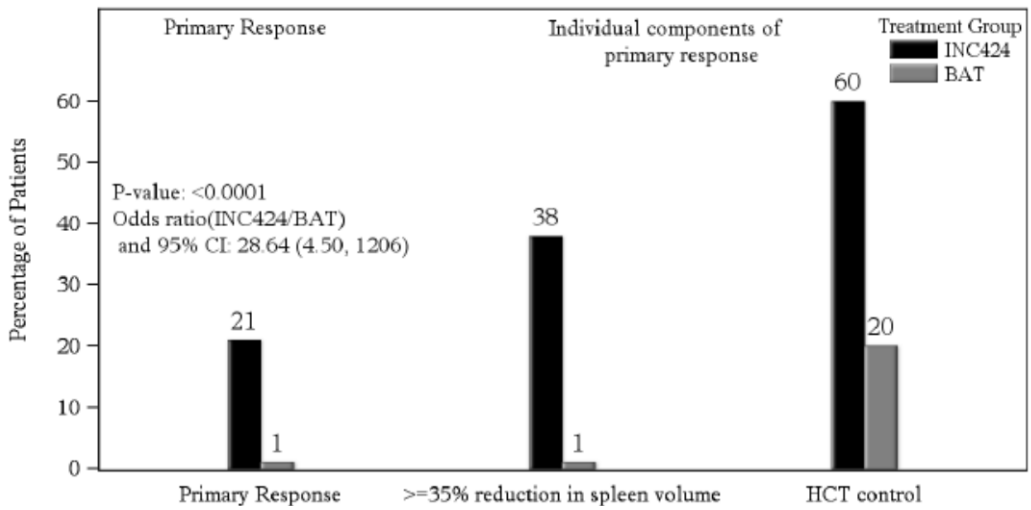
	Ruxolitinib N=110	BAT N=112
Patients achieving the primary response at Week 32 – n (%)	23 (20.9)	1 (0.9)
95% CI of the response rate	13.7, 29.7	0.0, 4.9
P-value	< 0.0001	
Odds ratio (ruxolitinib / BAT) and 95% CI	28.64 (4.50, 1206)	
Difference in response rates (ruxolitinib-BAT) and 95% CI	20.02 (12.22, 27.82)	

Primary response was defined as both the absence of eligibility for phlebotomy and at least 35% reduction from baseline in spleen volume.

Table 13. Individual components of the primary response at week 32 by treatment group

	INC424 N=110	BAT N=112
Spleen volume reduction from baseline >= 35% at Week 32		
Number of subjects	42 (38.18)	1 (0.89)
95% CI	(29.1, 47.9)	(0.0, 4.9)
Absence of phlebotomy eligibility		
Number of subjects	66 (60.00)	22 (19.64)
95% CI	(50.2, 69.2)	(12.7, 28.2)

Figure 2. Percent of patients achieving the primary response and components of the primary response at Week 32 (FAS – Study B2301)



Primary response results at Week 32 by subgroups and strata are reported in Table 14 and Table 15, respectively.

Table 14. Percent of subjects achieving the primary response at Week 32 by subgroups in the Ruxolitinib arm (Study B2301)

	INC424		
Subgroup	N	No. of responders (%)	95% CI of the response rate
HU intolerance	59	13 (22.03)	(12.29, 34.73)
HU resistance	51	10 (19.61)	(9.82, 33.12)
Baseline palpable splenomegaly: <10cm	71	19 (26.76)	(16.94, 38.59)
Baseline palpable splenomegaly: >=10cm	37	4 (10.81)	(3.03, 25.42)
Male	66	13 (19.70)	(10.93, 31.32)
Female	44	10 (22.73)	(11.47, 37.84)
Age group <60 years	49	10 (20.41)	(10.24, 34.34)
Age group >=60 years	61	13 (21.31)	(11.86, 33.68)
Region: US	18	4 (22.22)	(6.41, 47.64)
Region: non-US	92	19 (20.65)	(12.92, 30.36)
Race: White/Caucasian	98	19 (19.39)	(12.10, 28.61)
Race: Other	12	4 (33.33)	(9.92, 65.11)
Ethnicity: Hispanic/Latino	7	3 (42.86)	(9.90, 81.59)
Ethnicity: Other	103	20 (19.42)	(12.28, 28.38)

Table 15. Patients achieving the primary response at Week 32, by stratum (HU resistance or HU intolerance) (FAS – Study B2301)

Stratum	N	Responders n (%)	95% CI of the response rate
		Ruxolitinib	
HU resistance	51	10 (19.61)	(9.82, 33.12)
HU intolerance	59	13 (22.03)	(12.29, 34.73)
		BAT	
HU resistance	51	1 (1.96)	(0.05, 10.45)
HU intolerance	61	0	NA
		Odds ratio and 95% CI ruxolitinib-BAT	**Difference in response rate and 95% CI ruxolitinib-BAT**
HU resistance		11.96 (1.59, 539.56)	17.65 (-2.71, 36.95)
HU intolerance		NA	22.03 (4.61, 39.25)

Primary response was defined as both absence of phlebotomy eligibility and at least 35% reduction from baseline in spleen volume.

Key secondary endpoints

- ***Durable primary response***

Among the 23 patients randomized to ruxolitinib who had achieved primary response, 22 maintained the response through data cut-off (15-Jan-2014). Results in terms of durable primary response at Week 48 are shown in Table 16.

Table 16. Durable primary response at Week 48 (FAS - Study B2301)

	Ruxolitinib N=110	BAT N=112
Patients maintaining primary response at Week 48 - n (%)	21 (19.1)	1 (0.9)
95% CI of the response rate	(12.2, 27.7)	(0.0, 4.9)
P-value	< 0.0001	
Odds ratio ruxolitinib / BAT and 95% CI	26.11 (3.98, 1080)	
Difference in response rates ruxolitinib-BAT and 95% CI	18.19 (10.64, 25.73)	

Durable primary response was defined as both durable hematocrit control (absence of phlebotomy eligibility) and durable reduction in spleen volume (at least 35% reduction from baseline).

- ***Complete Haematological remission***

Complete haematological remission results are summarized in Table 17.

Table 17. Complete haematologic remission at Week 32 – analysis adjusted on WBC/platelet status* (FAS - Study B2301)

	Ruxolitinib N=110	BAT N=112
Patients achieving complete hematological remission at Week 32 – n (%)	26 (23.6)	10 (8.9)
95% CI of the response rate	(16.1, 32.7)	(4.4, 15.8)
P-value	0.0028	
Odds ratio ruxolitinib / BAT and 95% CI	3.35 (1.43, 8.35)	
Difference in response rates ruxolitinib-BAT and 95% CI	15.06 (5.74, 24.38)	

*P-value, odds ratio and 95% CI were calculated using stratified exact Cochran-Mantel-Haenszel test by adjusting for the WBC/platelet status (abnormal vs normal) at baseline. WBC/Platelet status was defined as abnormal if WBC count was > 15×10^9/L. and/or platelet count > 600×10^9/L.

Other secondary endpoints

Overall clinicohematologic response

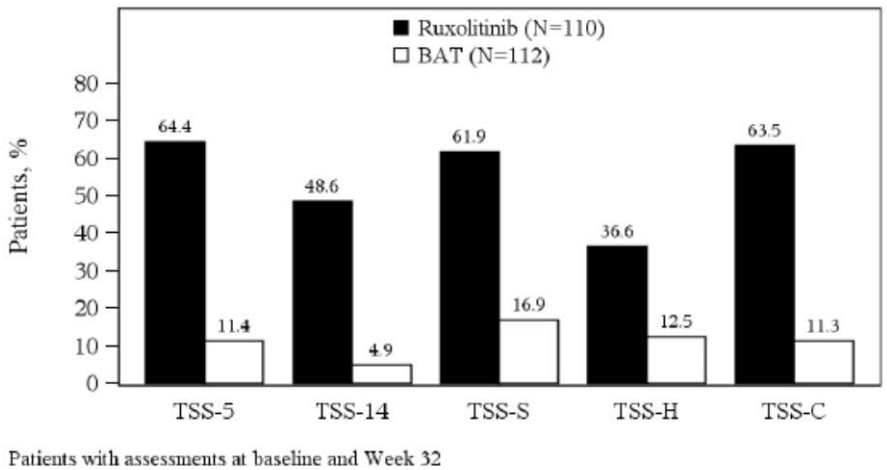
Differences were also seen regarding overall clinicohematologic response. Complete and partial responses at Week 32 were seen in 8% and 56% vs. 1% and 19% of subjects in the experimental and control arm, respectively (data not shown).

Exploratory endpoints

- ***Patient-reported outcomes***

In terms of Quality of Life, the rate of subjects achieving at least 50% reduction in TSS-14 and TSS-5 of MPN-SAF diary at Week 32 was 48.6% and 64.4% in the ruxolitinib arm, respectively; in the BAT arm, the rate of patients achieving at least 50% reduction in TSS-14 and TSS-5 was 4.9% and 11.4%, respectively (Figure 3).

Figure 3. Percent of patients achieving at least 50 % reduction in MPN-SAF total symptom scores at Week 32 (FAS)



Patients with assessments at baseline and Week 32

Ruxolitinib: n=	73	74	63	71	74
BAT: n=	79	81	71	80	80
OR (95% CI)	14.41	18.12	7.92	4.03	13.95
Ruxolitinib/BAT	(5.69, 36.73)	(5.73, 72.71)	(3.34, 19.33)	(1.66, 10.10)	(5.56, 35.40)

TSS-14=All 14 items are listed in [Study B2301-Appendix 16.1.1-Protocol-Appendix 8]
TSS-5: items include itching, fullness/early satiety, headache, muscle ache, and night sweats
TSS-S: items include abdominal discomfort, and fullness/early satiety
TSS-H: items include vision problems, dizziness, concentration problems, headache, numbness/tingling, ringing in ears, and skin redness
TSS-C: Items include tiredness, itching, muscle aches, night sweats, and sweats while awake
MPN-SAF=Myeloproliferative neoplasm Symptom Assessment Form, BAT=Best available therapy.
Source: [SCE Appendix 1-Figure 3.2-1].

The results of Patient Global Impression of Change (PGIC) questionnaire has shown that 66% of patients in the experimental arm reported an improvement at Week 4 *versus* 19% in the control arm. At week 32 the improvement in perception of treatment benefit was 78% in patients treated with ruxolitinib *versus* 33% of the BAT arm (data not shown).

Change in overall quality-of-life was measured by the EORTC QLQ-C30. At Week 32, patients randomized to ruxolitinib showed improvement in Global Health Status and in all 5 functioning subscales of the EORTC QLQ-C30 while patients randomized to BAT showed minimum changes in all subscales (Table 18).

Table 18. Change in EORTC QLQ-C30 score from Baseline to Week 32 (FAS)

EORTC QLQ-C30 score	Ruxolitinib			BAT		
	n[a]	Baseline	Mean change in score from Baseline to Week 32	n[a]	Baseline	Mean change in score from Baseline to Week 32
Global health status/QoL	89	59.6	10.9	83	64.6	-4.8
Functional Scales						
Physical Functioning	90	80.0	6.4	84	83.2	-1.5
Role Functioning	88	78.4	5.3	81	78.2	-0.41
Emotional Functioning	88	75.9	7.9	80	77.4	1.0
Cognitive Functioning	88	76.7	4.2	80	77.9	-3.3
Social Functioning	87	81.4	7.7	80	81.3	-0.42
Symptom scales						
Fatigue	89	37.7	-12.2	81	36.8	0.82
Nausea and Vomiting	89	5.2	-1.5	80	4.8	0.21
Pain	86	25.4	-11.1	80	24.4	0.21
Single item scales						
Dyspnoea	89	22.5	-6.0	80	19.6	2.5
Insomnia	89	27.0	-12.0	81	37.0	-7.8
Appetite Loss	88	12.5	-10.2	81	15.6	-0.82
Constipation	88	14.4	-2.7	80	13.3	1.7
Diarrhoea	87	12.6	-3.8	80	9.6	2.9
Financial Difficulties	87	17.6	-5.4	80	14.6	1.3

a. n is the number of patients with both baseline and post-baseline at the timepoint
For Global health status/QoL and Functional scales positive values for mean change indicate improvement, and for the symptoms and the single item scale negative values for mean change indicate improvement
EORTC QLQ-C30 score=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
BAT=Best available therapy
Source: [Study B2301-Table 14.2-16.3]

- **Evaluation of cytokines and other plasma proteins marker levels**

Three cytokine markers examined (interleukin-1 beta, tumor necrosis factor alpha, and interleukin-6) all presented with more than 60% of the sample for both ruxolitinib and BAT treatment groups having values below the lower level of quantitation. Therefore these markers could not be analyzed for treatment effects. Interesting differences in changes were seen in plasma levels of CRP, soluble receptors (ICAM-1, soluble CD40, TNFRII, and VCAM-1), myeloperoxidase (MPO), and leptin between the respective treatment arms (data not shown).

Ancillary analyses

N/A

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of Efficacy for trial B2301

Title: A Randomized, open label, two arm, multicenter phase III study comparing the efficacy and safety of ruxolitinib to best available therapy (BAT) in patients with polycythemia vera (PV) who are resistant to or intolerant of hydroxyurea:			
Study identifier	CINC424B2301 (B2301)		
Design	Phase 3, open label, randomized (1:1), two-arm, multicentre study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		32 weeks N/A Maximum 208 weeks (4 years)
Hypothesis	Superiority		
Treatment groups	Experimental arm (Ruxolitinib)		Ruxolitinib starting dose 10 mg BID, then adjusted (max. 25 mg bid, min. 5 mg per day); 110 patients randomized
	Control arm (BAT)		BAT doses and administration were according to manufacturer's instructions and could be adjusted based on Investigator judgment; 112 patients randomized
Endpoints and definitions	Primary endpoint	Primary response	Proportion of subjects achieving a response at Week 32, with response defined as having achieved both of the following: the absence of phlebotomy eligibility beginning at the Week 8 visit and continuing through Week 32, with no more than one phlebotomy eligibility occurring post-randomization and prior to the Week 8 visit; a reduction in spleen volume as assessed by Imaging ≥ 35% from baseline at Week 32.
	Secondary endpoint	Durable primary response	Proportion of subjects maintaining primary response at Week 48
	Secondary endpoint	Complete haematological remission	Proportion of subjects achieving complete haematological remission at Week 32 (hematocrit control, platelet count ≤ 400×10^9/L, WBC ≤ 10×10^9/L)
Database lock	15 January 2014		

Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Intent to treat (cut-off date at 15 January 2014); all randomized patients: 222		
Descriptive statistics	Treatment group	Ruxolitinib	BAT

and estimate variability	Number of subjects	110	112
	Primary response W32 n (%)	23 (20.9)	1 (0.9)
	95% CI	(13.7 – 29.7)	(0.0 – 4.9)
	Durable primary response (%)	19.1	0.9
	95% CI	(12.2 – 27.2)	(0.0 – 4.9)
	Complete haematological remission (%)	23.6	8.9
	95% CI	(16.1 – 32.7)	(4.4 – 15.8)
Effect estimate per comparison	Primary endpoint (Primary response)	Comparison groups	Ruxolitinib vs BAT
		Odds ratio	28.64
		95% CI	(4.50, 1206)
		P-value	<0.0001
	Secondary endpoint (Durable primary response)	Comparison groups	Ruxolitinib vs BAT
		Odds ratio	26.11
		95% CI	(3.98, 1080)
		P-value	<0.0001
	Secondary endpoint (Complete haematological remissoin)	Comparison groups	Ruxolitinib vs BAT
		Odds ratio	3.35
		95% CI	(1.43, 8.35)
		P-value	0.0028
Notes	Stratification factors: HU resistance ; HU intolerance		

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study

Study INCB 18424-256

This was a phase 2, multicenter, open-label, randomized, 2-part study of ruxolitinib administered to subjects with PV or Essential Thrombocythemia (ET) who were refractory to or intolerant of hydroxyurea (HU) or for whom treatment with HU was contraindicated (First patient enrolled 29-AUG-2008; data cut-off date 15-MAR-2013).

In the initial (dose-finding) phase of the study, subjects in each disease group (PV or ET) were randomized independently in a 1:1:1 ratio to receive ruxolitinib 10 mg twice daily (BID), 25 mg BID, or 50 mg once daily (OD). Six to 8 subjects per disease group were assigned to each treatment regimen, and subjects were to remain on the initial treatment regimen for a minimum of 8 weeks (two 4-week cycles); dose adjustments were allowed only for safety reasons during this time.

Patients with PV refractory to or intolerant of HU treatment, or for whom HU treatment was contraindicated were included in the study. Subjects must have had an ECOG performance status ≤ 2 and met the following baseline laboratory requirements: HTC > 45% or phlebotomy required twice in the 6 months before the study, with at least 1 occurrence in the 3 months before treatment with ruxolitinib; platelet count ≥ 125 × 10^9/L; ANC ≥ 1.2 × 10^9/L. Subjects must not have had a history of other malignancies, evidence of reoccurrence or clinically significant cardiac disease.

After completion of the dose-finding phase of the study the starting dose of ruxolitinib for the expansion phase was determined to be 10 mg BID for subjects with PV. After subjects completed 8 weeks of ruxolitinib treatment at the starting dose, investigators were permitted to adjust the dose for toxicity (interruption or reduction, with rechallenge after interruption) or lack of efficacy (dose increases may have occurred in ≥ 5 mg increments up to a maximum total daily dose of 75 mg). Administration of single-agent ruxolitinib continued until a subject met a withdrawal criterion, reached an intolerable toxicity, had progression of disease, or withdrew consent.

The efficacy results in terms of haematocrit control and/or reduced palpable spleen size are reported in Table 20.

Table 20.Summary of Subjects With PV Who Achieved Hematocrit Control and/or Reduced Palpable Spleen Size Over Time (ITT/PV Subjects – Study INCB 18424-256)

Timepoint	Hct < 45% Without Phlebotomy From Week 4 Through the Timepoint (n = 34)	≥ 50% Reduction in Palpable Splenomegaly (n = 25)[a,b]	Hct < 45% Without Phlebotomy and ≥ 50% Reduction in Palpable Splenomegaly (n = 25)[a,b]
Week 12	31 (91.2)	16 (64.0)	13 (52.0)
Week 32	32 (94.1)	NA[c]	NA[c]
Week 36	32 (94.1)	17 (68.0)	15 (60.0)
Week 48	27 (79.4)	17 (68.0)	12 (48.0)
Week 96	25 (73.5)	16 (64.0)	13 (52.0)
Week 144	23 (67.7)	17 (68.0)	12 (48.0)
Week 192	23 (67.7)	17 (68.0)	12 (48.0)

Note: Week 12 = Cycle 4 Day 1; Week 32 = Cycle 9 Day 1; Week 36 = Cycle 10 Day 1; Week 48 = Cycle 13 Day 1; Week 96 = Cycle 25 Day 1; Week 144 = Cycle 37 Day 1; and Week 192 = Cycle 49 Day 1.

[a] Includes subjects who achieved nonpalpable spleen.

[b] Subjects with abnormal but missing assessments of spleen length at baseline were included in the denominator. Note: Two subjects had abnormal but missing baseline spleen length assessments.

[c] NA = not applicable. Spleen assessments were performed every 12 weeks starting at Week 24; therefore, data were not collected at Week 32 but are presented for Week 36.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A randomised, open-label, active-controlled phase 3 study (RESPONSE) was conducted in 222 patients with PV who were resistant to or intolerant of hydroxyurea as defined based on the European LeukemiaNet (ELN) international working group published criteria. 110 patients were randomised to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses

were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8) and observation (15.3%) (see SmPC section 5.1).

Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (>80%) had received at least two phlebotomies in the last 24 weeks prior to screening. Comparative data regarding long-term survival and incidence of disease complications is missing (see SmPC section 5.1).

The primary composite endpoint was the proportion of patients achieving both an absence of phlebotomy eligibility (HCT control) and a ≥ 35% reduction in spleen volume from baseline at week 32. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and remained free from progression at week 48, as well as the proportion of patients achieving complete haematological remission at week 32(see SmPC section 5.1).

By using resistance or intolerance to hydroxyurea (HU) as a key inclusion criterion (both in phase2 study 256 and phase 3 B2301), only PV patients with an established need for cytoreductive therapy were being selected as a target population. In the study the definition of HU resistance or intolerance was based on the modified European Leukemia Net (ELN) defined criteria for HU resistance/intolerance (Barosi et al 2009; Barosi et al 2013). After the revision of the inclusion criteria following the 1st amendment of the protocol, the recruitment base for the study was significantly widened.

Efficacy data and additional analyses

The primary endpoint was achieved in 20.9% and 0.9% of the subjects in the experimental and control arm, respectively (OR 28.64; 95% CI 4.50 –1206, p<0,001). At the same time point (week 32), haematocrit control was achieved in 60% of patients in the ruxolitinib arm compared to 19.6% in the BAT arm, and spleen volume reduction >35% occurred in 38.2 vs 0.9%, in the respective arms. Thus, for the primary endpoint the largest difference between the arms lay in achievement of spleen size reduction. At Week 48, 54.5% of the patients randomized to ruxolitinib maintained a durable haematocrit control and 35.5% maintained a durable spleen volume reduction.

The proportions of patients randomized to ruxolitinib who achieved the primary response at Week 32 were compared for some subgroups in the ruxolitinib arm. Gender, age (< or >60y), and whether the subject was resistant or intolerant to HU did not seem to affect the rate of primary response towards ruxolitinib. No statistically significant association between response rate and baseline spleen volume could be confirmed by using a logistic regression based on baseline spleen volume, in spite of the finding among patients with a baseline palpable splenomegaly < 10 cm that 27% (19/71) achieved the primary efficacy endpoint compared to 11% (4/37) for patients with a baseline palpable splenomegaly ≥ 10 cm.

During the assessment the CHMP raised a major objection about the indication needing to be further discussed, with reference to early HU resistance. The definition of HU resistance made possible the enrolment of patients with early failure on HU, e.g. only in terms of infrequent phlebotomies and non-symptomatic splenomegaly and the benefit of switching to ruxolitinib in these patients was questioned. The Applicant has presented data indicating a meaningful clinical activity of ruxolitinib in PV across various subgroups constituted by subjects with more or less pronounced failure or resistance to HU. There is a trend towards fewer responses in patients with more advanced disease but this may also reflect a general pattern with advanced malignancy often being more recalcitrant. Still, there is a significantly higher proportion of responses seen with ruxolitinib vs. BAT in this population. Within the

study population it was also found that patients with “early HU resistance” often had other characteristics indicative of advanced PV disease. For example, the majority of these patients had elevated WBC and PLT counts as discrete signs of uncontrolled myeloproliferation associated with an increased risk of thrombosis and bleeding, respectively. It is acknowledged that these are not recognized sub-groups within a patient population that fail HU. Furthermore, the reasons given for modifying parts of the ELN criteria was accepted (e.g., the omission of symptomatic splenomegaly). At the present, the ELN criteria may be useful as an instrument for detecting anti-proliferative properties of drugs intended for use in PV, but cannot be regarded as therapeutic guidelines. Aside from established and proposed risk factors in PV (11), a high age and other patient related factors e.g comorbidities may sometimes call for individualization of therapy.

For the majority of results reported the treatment duration was <1 year. Long-term effects are of critical importance, especially if treatment is started early in PV, eg due to failure of achieving complete haematological remission or haematocrit control with HU in accordance with ELN criteria. Long-term efficacy of ruxolitinib needs to be further elucidated since the potential lack of efficacy in the long term raises concern with respect to the maintenance of a positive benefit-risk balance in the applied indication This pertain to (late) achievement of response and duration of (various) responses. To further support this, the MAH will submit interim Week 80 CSR data and a final CSR will be generated when all patients will have completed the Week 208 visit or discontinued in order to support the long-term effects of ruxolitinib (see conclusions on clinical efficacy).

Though the pattern of responses to ruxolitinib appears consistent from the aspect of variable patient baseline characteristics, there may exist a small percentage of patients with an “aberrant” response. This is illustrated by a few patients with an increase, sometimes transient, in spleen volume after initiation of ruxolitinib treatment. A similar small group of “outliers” is found among individual white blood cell (WBC) responses where a few patients starting from a normal or near normal values develop a paradoxical and very pronounced increase in WBC. Since these findings seem very discrete and hardly affect the general pattern the CHMP recommended the MAH to further discuss it as part of the week 80 CSR of study Week 80 CSR of study B2301.

Crossing over from the BAT to the ruxilitinib arm was allowed after Week 32, and by Week 48 almost all patients randomized to BAT (106/112; 94.6%) had discontinued their randomized treatment (the majority crossed-over to ruxolitinib). A total of 13.6% (15/110) of the patients randomized to ruxolitinib had discontinued their treatment. Hence, for data recorded after Week 32 the Study B2301 is in effect no longer a 2-armed study. The vast majority of patients in the BAT arm (87%) discontinued due to lack of efficacy. Regarding this point, it is noted that the Protocol did not stipulate stop of ruxolitinib treatment in case of a relative loss of efficacy (whereas patients in the BAT arm were allowed to cross over after Week 32 if they did not reach the primary endpoint or lost an initial response).

Regarding the secondary endpoints, achievement of complete haematological remission at Week 32 was reached by 23.6 and 8.9% of patients in the ruxolitinib and BAT arm, respectively (OR 3.35; 95% CI 1.43 –8.35, p=0.0028). Differences were also seen regarding overall clinicohematologic response. Complete and partial responses at Week 32 were seen in 8% and 56% vs. 1% and 19% of subjects in the experimental and control arm, respectively. These responses were mostly durable at Week 48 and clearly favoured Ruxolitinib treatment.

Furthermore, significantly more patients randomized to ruxolitinib achieved a complete haematological remission (haematocrit control, platelet count $\leq$ 400$\times$109/L, and WBC count $\leq$ 10$\times$109/L) at Week 32 when compared to patients randomized to BAT: 23.6% vs 8.9%, respectively (p=0.0028, when adjusted for baseline platelet and WBC status).

In terms of Quality of life, consistently more patients randomized to ruxolitinib reported less severe symptoms at Week 32 in MPN-SAF total and sub-scores compared to patients randomized to BAT. Improvements in Global Health Status and in all 5 functioning subscales of the EORTC QLQ-C30 also favoured the Ruxolitinib arm.

Finally, dynamic changes were seen following ruxolitinib treatment in plasma levels of CRP, soluble receptors (ICAM-1, soluble CD40, TNFRII, and VCAM-1), myeloperoxidase (MPO), and leptin. Based on this, the CHMP recommended the MAH to provide further analyses as part of the forthcoming reports from study B2301 (week 80 and week 208 CSRs) and explore the changes in these parameters in a more highly resolved temporal scale (eg daily analyses after initiation of therapy) as well as on long term in order to define whether any of these biomarkers could be useful in the clinical monitoring of PV during ruxolitinib treatment.

2.4.4. Conclusions on the clinical efficacy

Study B2301 provided convincing evidence of clinical efficacy of ruxolitinib in terms of the primary endpoint primary response compared to BAT in patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea. However further follow-up is still requested regarding long-term effects . Long-term efficacy of ruxolitinib needs to be further elucidated since the potential lack of efficacy in the long term raises concern with respect to the maintenance of a positive benefit-risk balance in the applied indication

The CHMP considers the following measures necessary to address issues related to efficacy:

Long-term efficacy and safety of ruxolitinib including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301 should be provided. Regarding long-term effects, an interim Week 80 CSR will be available in June 2015. A final CSR will be generated when all patients will have completed the Week 208 visit or discontinued (December 2019).

2.5. Clinical safety

Introduction

The safety of ruxolitinib was investigated in 855 subjects from 2 studies performed in patients with polycytemia vera (PV) (Study B2301, cut-off 15-Jan-2014; Study 256, cut-off 15-Mar-2013) and the following 3 studies performed in patients with myelofibrosis (MF):

- Study CINCB 18424-351, a randomized double-blind, placebo-controlled study of the Janus kinase (JAK) inhibitor INC424 tablets administered orally to patients with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF), or post-essential thrombocythemia myelofibrosis (PET-MF) (data cut-off date: 02-Sep-2013)
- Study CINC424A2352, a randomized study of the JAK inhibitor INC424 tablets compared to best available therapy (BAT) in patients with PMF, PPV-MF or PET-MF (data cut-off date: 01-Sep-2013)
- Study INCB 18424-251, a Phase I/II, open-label study of the JAK2-inhibitor INCB018424 administered orally to patients with PMF, PPV-MF, or PET-MF (data cutoff date: 01-Oct-2012)

However data from the Phase III Study B2301 was considered key for assessing the safety aspects for the proposed indication. This dataset includes safety data presented up to Week 32 from patients with PV randomized to ruxolitinib or BAT in Study B2301. Due to a larger than expected imbalance of exposure at the date of data cut-off in Study B2301 and in order to conduct an adequate comparative assessment of the safety profiles, analyses of the Phase III PV patient population up to Week 32 were conducted based

on comparative exposures during the period from Day 1 to the Week 32 visit, i.e. before the vast majority of BAT patients crossed over to ruxolitinib as per study protocol.

Study B2301 (RESPONSE)

Patient exposure

In study B2301, through Week 32, cumulative doses and dose intensity varied based on type of ruxolitinib dose adjustments in the experimental arm and regimen used in the BAT arm. The exposure to study drug up to Week 32 (SAS) is presented in table 21.

Table 21. Exposure to study drug up to Week 32 (SAS - Study B2301)

	Ruxolitinib N=110 n (%)	BAT N=111 n (%)
Duration of exposure (week)		
Mean (SD)	31.9 (7.04)	32.2 (5.52)
Median (min-max)	34.1 (1.1 - 34.1)	34.0 (2.1 - 34.1)
Patient-years	67.28	68.50
Cumulative dose (mg)		
Mean (SD)	5397(2037.4)	-
Median (min-max)	5265.0 (55-10065)	-
Dose intensity (mg/day)		
Mean (SD)	23.8 (7.13)	-
Median (min-max)	22.3 (7-42)	-

For Week 32, data up to Day 239 are included.
Dose intensity (mg/day) = Cumulative dose (mg)/Duration of exposure (day).
Source: Table 14.3-1.8 and Table 14.3-1.7

For the duration of the study up to data cut-off (15-Jan-2014), the mean and median duration of exposures were approximately 81 weeks in the ruxolitinib arm, and approximately 34 weeks in the BAT arm, the ratio for cumulative (patient-years) exposure of ruxolitinib to BAT was 2.33 (169.97/72.81).

Adverse events

An overview of treatment-emergent adverse events up to Week 32 and up to data cut-off is presented in Table 22 and Table 23, respectively.

Table 22. Overview of treatment-emergent AEs up to Week 32 (SAS - Study B2301)

	Ruxolitinib N=110 n (%)	BAT N=111 n (%)
Any AE	105 (95.5)	104 (93.7)
Any grade 3-4 AE	36 (32.7)	32 (28.8)
Any treatment-related AE	65 (59.1)	37 (33.3)
Any SAE	15 (13.6)	10 (9.0)
AEs leading to discontinuation of treatment	7 (6.4)	1 (0.9)

Table 23. Overview of treatment-emergent AEs up to data cut-off (SAS - Study B2301)

	Ruxolitinib N=110 n (%)	BAT N=111 n (%)
Any AE	110 (100)	106 (95.5)
Any grade 3-4 AE	49 (44.5)	32 (28.8)
Any treatment-related AE	78 (70.9)	39 (35.1)
Any SAE	26 (23.6)	10 (9.0)
AEs leading to discontinuation of treatment	9 (8.2)	2 (1.8)[a]

Data collected after crossover for patients randomized to BAT who crossed over to ruxolitinib were not included.
a. 6 additional patients changed the BAT selected by the Investigator at randomization to another BAT, due to AEs, as allowed per protocol (Section 10.1.1).

Frequent adverse events regardless causality up to Week 32 and up to data cut-off are reported by preferred term in Table 24 and Table 25.

Table 24. Frequent AEs (at least 5% in any group) by preferred term up to Week 32 (SAS - Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**105 (95.5)**	**36 (32.7)**	**104 (93.7)**	**32 (28.8)**
Anaemia	20 (18.2)	1 (0.9)	3 (2.7)	0
Headache	18 (16.4)	1 (0.9)	21 (18.9)	1 (0.9)
Diarrhoea	16 (14.5)	0	8 (7.2)	1 (0.9)
Fatigue	16 (14.5)	0	17 (15.3)	3 (2.7)
Pruritus	15 (13.6)	1 (0.9)	25 (22.5)	4 (3.6)
Dizziness	13 (11.8)	0	11 (9.9)	0
Muscle spasms	13 (11.8)	1 (0.9)	5 (4.5)	0
Dyspnoea	11 (10.0)	3 (2.7)	2 (1.8)	0
Abdominal pain	10 (9.1)	1 (0.9)	13 (11.7)	0
Nasopharyngitis	10 (9.1)	0	9 (8.1)	0
Constipation	9 (8.2)	0	3 (2.7)	0
Cough	9 (8.2)	0	6 (5.4)	0
Thrombocytopenia	9 (8.2)	4 (3.6)	12 (10.8)	2 (1.8)
Arthralgia	8 (7.3)	0	7 (6.3)	1 (0.9)
Asthenia	8 (7.3)	2 (1.8)	12 (10.8)	0
Epistaxis	7 (6.4)	0	3 (2.7)	0
Herpes zoster	7 (6.4)	0	0	0
Nausea	7 (6.4)	0	4 (3.6)	0
Oedema peripheral	7 (6.4)	0	7 (6.3)	0
Abdominal pain upper	6 (5.5)	0	5 (4.5)	1 (0.9)
Back pain	6 (5.5)	1 (0.9)	4 (3.6)	0
Gamma-glutamyltransferase increased	6 (5.5)	4 (3.6)	3 (2.7)	0
Haematoma	6 (5.5)	0	3 (2.7)	0
Night sweats	6 (5.5)	0	9 (8.1)	0
Tinnitus	6 (5.5)	2 (1.8)	3 (2.7)	0
Weight increased	6 (5.5)	0	1 (0.9)	0
Insomnia	5 (4.5)	1 (0.9)	6 (5.4)	1 (0.9)
Myalgia	5 (4.5)	0	8 (7.2)	0
Paraesthesia	5 (4.5)	0	7 (6.3)	0
Bone pain	3 (2.7)	0	6 (5.4)	1 (0.9)
Decreased appetite	3 (2.7)	0	6 (5.4)	0

Preferred terms are sorted by descending frequency of ruxolitinib all grades column.

Table 25. Frequent AEs (at least 5% in any group) by preferred term up to data cut-off (SAS - Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**110 (100)**	**49 (44.5)**	**106 (95.5)**	**32 (28.8)**
Anaemia	27 (24.5)	2 (1.8)	4 (3.6)	0
Headache	23 (20.9)	2 (1.8)	21 (18.9)	1 (0.9)
Diarrhoea	21 (19.1)	0	9 (8.1)	1 (0.9)
Fatigue	19 (17.3)	0	17 (15.3)	3 (2.7)
Pruritus	19 (17.3)	1 (0.9)	25 (22.5)	4 (3.6)
Dizziness	15 (13.6)	0	11 (9.9)	0
Dyspnoea	15 (13.6)	3 (2.7)	2 (1.8)	0
Muscle spasms	15 (13.6)	1 (0.9)	5 (4.5)	0
Arthralgia	13 (11.8)	0	8 (7.2)	1 (0.9)
Cough	13 (11.8)	0	6 (5.4)	0
Nasopharyngitis	13 (11.8)	0	9 (8.1)	0
Thrombocytopenia	13 (11.8)	4 (3.6)	12 (10.8)	2 (1.8)
Weight increased	13 (11.8)	0	1 (0.9)	0
Abdominal pain	12 (10.9)	2 (1.8)	13 (11.7)	0
Constipation	12 (10.9)	1 (0.9)	3 (2.7)	0
Herpes zoster	11 (10.0)	2 (1.8)	0	0
Hypertension	11 (10.0)	2 (1.8)	3 (2.7)	1 (0.9)
Asthenia	10 (9.1)	2 (1.8)	12 (10.8)	0
Back pain	10 (9.1)	1 (0.9)	5 (4.5)	0
Night sweats	10 (9.1)	0	9 (8.1)	0
Pyrexia	10 (9.1)	0	5 (4.5)	0
Nausea	9 (8.2)	0	4 (3.6)	0
Oedema peripheral	9 (8.2)	0	7 (6.3)	0
Abdominal pain upper	8 (7.3)	0	5 (4.5)	1 (0.9)
Epistaxis	8 (7.3)	0	3 (2.7)	0

Gamma-glutamyltransferase increased	8 (7.3)	7 (6.4)	3 (2.7)	0
Haematoma	8 (7.3)	0	3 (2.7)	0
Pain in extremity	8 (7.3)	1 (0.9)	4 (3.6)	0
Urinary tract infection	8 (7.3)	2 (1.8)	0	0
Bronchitis	7 (6.4)	0	4 (3.6)	0
Upper respiratory tract infection	7 (6.4)	0	5 (4.5)	0
Basal cell carcinoma	6 (5.5)	4 (3.6)	1 (0.9)	1 (0.9)
Influenza	6 (5.5)	0	2 (1.8)	0
Tinnitus	6 (5.5)	2 (1.8)	3 (2.7)	0
Vertigo	6 (5.5)	0	4 (3.6)	0
Insomnia	5 (4.5)	1 (0.9)	6 (5.4)	1 (0.9)
Myalgia	5 (4.5)	0	8 (7.2)	0
Paraesthesia	5 (4.5)	0	7 (6.3)	0
Decreased appetite	4 (3.6)	1 (0.9)	6 (5.4)	0
Bone pain	3 (2.7)	0	6 (5.4)	1 (0.9)

Preferred terms are sorted by descending frequency of ruxolitinib all grades column.
Data collected after crossover for patients randomized to BAT who crossed-over to ruxolitinib are not included in this table.

Due to the higher HU exposure in baseline characteristics of ruxolitinib treated patients, the rate of AEs were adjusted for exposure. The adjusted rate of all AEs per 100 patient-years were 64.7% in the ruxolitinib arm *vs* 145.6% in the BAT arm and rates of grade 3-4 AEs were 28.8% *vs* 44.0%, respectively. The main differences in exposure-adjusted rates between the ruxolitinib arm and the BAT arm are reported below: anaemia (15.5% *vs* 5.5%), dyspnoea (8.8% *vs* 2.7%), weight increase (7.6% *vs* 1. 4%), herpes zoster (6.5% *vs* 0%), hypertension (6.5% *vs* 4.1%), pruritus (11.2% *vs* 34.3%), headache (13.5% *vs* 28.8%), fatigue (11.2% *vs* 23.3%), thrombocytopenia (7.6% *vs* 16.5%), dizziness (8.8% *vs* 15.1%), diarrhoea (12.4% *vs* 12.4%), epistaxis (4.7% *vs* 4.1%).

Frequent adverse events suspected to be related to study drug up to Week 32 and up to data cut-off are reported by preferred term in Table 26 and Table 27.

Table 26. Frequent AEs (at least 2% in any group) related to study drug up to Week 32 (SAS - Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**65 (59.1)**	**17 (15.5)**	**37 (33.3)**	**7 (6.3)**
Anaemia	19 (17.3)	0	1 (0.9)	0
Thrombocytopenia	8 (7.3)	3 (2.7)	7 (6.3)	1 (0.9)
Dizziness	7 (6.4)	0	0	0
Headache	7 (6.4)	1 (0.9)	0	0
Asthenia	4 (3.6)	2 (1.8)	5 (4.5)	0
Fatigue	4 (3.6)	0	2 (1.8)	1 (0.9)
Gamma-glutamyltransferase increased	4 (3.6)	2 (1.8)	1 (0.9)	0
Weight increased	4 (3.6)	0	1 (0.9)	0
Herpes zoster	3 (2.7)	0	0	0
Muscle spasms	3 (2.7)	1 (0.9)	0	0
Nausea	3 (2.7)	0	2 (1.8)	0

Preferred terms are sorted by descending frequency of ruxolitinib all grades column.

Table 27. Frequent AEs (at least 5% in any group) related to study drug up to cut-off (SAS - Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**78 (70.9)**	**21 (19.1)**	**39 (35.1)**	**7 (6.3)**
Anaemia	24 (21.8)	1 (0.9)	1 (0.9)	0
Thrombocytopenia	12 (10.9)	3 (2.7)	7 (6.3)	1 (0.9)
Weight increased	9 (8.2)	0	1 (0.9)	0
Dizziness	8 (7.3)	0	0	0
Headache	8 (7.3)	2 (1.8)	0	0
Asthenia	6 (5.5)	2 (1.8)	5 (4.5)	0
Fatigue	6 (5.5)	0	2 (1.8)	1 (0.9)

Preferred terms are sorted by descending frequency of ruxolitinib all grades column.
Data collected after crossover for patients randomized to BAT who crossed over to ruxolitinib are not included.

Adverse Events of special interest

Thrombocytopenia

In Study B2301 up to Week 32, the Standard MedDRA query (SMQ) of thrombocytopenia was reported in 8.2% of ruxolitinib-treated patients (grade 3-4: 3.6%) and all of these AEs were considered related to study drug; None led to discontinuation of therapy. Up to Week 32, the frequency of thrombocytopenia

reported in BAT-treated patients was 11.7%. In ruxolitinib treatment arm, decreased platelet counts values were reported in 24.5% (grade 3-4: 5.4%) of patients *vs* 18.9% in the BAT arm (grade 3-4: 3.6%). Twenty ruxolitinib-treated patients had platelet count <100 x 10^9/L, and none of these patients reported haemorrhage within 2 weeks of reaching the platelet threshold.

In the all PV patient population the SMQ of thrombocytopenia was reported in 14.2% of ruxolitinib-treated patients, of which 2.9% were of grade 3-4 severity; none of the patients discontinued ruxolitinib due to AE.

Anaemia

In Study B2301 43.6% of patients treated with ruxolitinib reported decreased haemoglobin (grade 3-4: 1.8%) *vs* 30.6% in the BAT treatment arm (no grade 3-4 haemoglobin abnormalities).

In the all PV patient population, haemoglobin abnormalities were reported in 58.8% of ruxolitinib treated patients (grade 3-4: 3.7%).

Infections

In Study B2301 up to Week 32 infections (excluding herpes zoster, urinary tract infections and tuberculosis) were reported in 32.7% ruxolitinib-treated patients and 34.2% BAT-treated patients. The most frequently reported infections in ruxolitinib-treated patients were nasopharyngitis (9.1%), and respiratory tract infection (2.7%).

In the randomised period of the pivotal studies in PV patients, one (0.9%) CTCAE grade 3 and no grade 4 urinary tract infection was reported in PV patients. The rate of herpes zoster was slightly higher in PV (6.4%) patients than in MF (4.0%) patients. There was one report of CTCAE grade 3 and 4 post-herpetic neuralgia amongst the PV patients (SmPC section 4.8).

Malignancies

There were 19 cases of secondary neoplasms reported during the randomized study period in the ruxolitinib arm and 4 cases in the BAT arm. After crossover to ruxolitinib 7 additional cases of second neoplasms were reported. Patients randomized to ruxolitinib with a medical history of neoplasm were 27.3% *vs* 20.5% of the BAT arm. Patients with second malignancies had 461.3 weeks of HU exposure (ruxolitinib arm) *vs* 206.9 weeks (BAT arm); patients without secondary malignancies had 145.7 weeks of HU exposure for ruxolitinib *vs* 142.4 weeks for BAT.

During the randomized treatment period up to the data cut-off, 8 patients treated with ruxolitinib and 2 patients treated with BAT developed non-melanoma skin cancer (NMSC). When adjusted for exposure, the rates of NMSC in patients randomized to ruxolitinib and those randomized to BAT were 4.7 and 2.7 per 100 patient-years, respectively. Two patients originally randomized to BAT developed NMSC after crossover to ruxolitinib. In 4 cases NMSC was diagnosed on Day 14, 22, 27 and 139 after starting ruxolitinib, respectively.

Bleeding

In the randomized period of the pivotal study in PV patients, bleeding events (including intracranial and gastrointestinal, bruising and other bleeding events) were reported in 20% of patients treated with ruxolitinib and 15.3% patients receiving best available therapy. Bruising was reported in similar frequencies in ruxolitinib and BAT arms (10.9% vs 8.1%). No intracranial bleeding and gastrointestinal haemorrhage events were reported in patients receiving ruxolitinib. One patient treated with ruxolitinib experienced a grade 3 bleeding event (post procedural bleeding); no grade 4 bleeding reported. Other bleeding events (including events such as epistaxis, post procedural haemorrhage, gingival bleeding)

were reported in 11.8% of patients treated with ruxolitinib and 6.3% treated with best available therapy (SmPC section 4.8).

Increased systolic blood pressure

In the phase 3 pivotal study in PV an increase in systolic blood pressure of 20 mmHg or more from baseline on at least one visit was recorded in 33.9 % of patients treated with ruxolitinib. At week 32, mean systolic BP increased by 0.65 mm Hg on the Jakavi arm, while it decreased by 2 mm Hg on BAT (SmPC section 4.8)..

Acute myeloid leukemia and myelofibrosis (and CMML)

During the randomized treatment period, 3 patients developed MF and one patient developed AML while on ruxolitinib treatment, compared to one patient who developed MF while on BAT. In addition, 2 patients randomized to BAT developed MF after crossover to ruxolitinib, one of whom progressed to AML. Additionally, one case of chronic myelomonocytic leukemia was reported in a patient after crossover to ruxolitinib. The interpretation of these cases is confounded by the advanced PV, the very long history of HU exposure and the early onset of these hematologic progressions after the start of ruxolitinib treatment in some of the cases. None of the cases were considered to be related to study medication by the Investigator.

Dyspnoea

Through the data cut-off date, dyspnoea was reported in 15 (13.6%) and exertional dyspnea was reported in 3 (2.7%) patients randomized to ruxolitinib, while dyspnoea was reported in 2 (1.8%) patients, and exertional dyspnea was reported in one (0.9%) patient randomized to BAT. Among the patients randomized to ruxolitinib, three had a grade 3 dyspnoea. Most of the patients had concurrent AEs that coincided with the onset of dyspnoea, such as pulmonary AEs (non-specified respiratory tract infection, pneumonia, coughing), cardiovascular AEs

Serious adverse event / deaths / other significant events

Serious Adverse Events (SAEs)

In the Study B2301, Through Week 32, 13.6% of the patients randomized to ruxolitinib and 9.0% in the patients randomized to BAT had at least one SAE. None of the SAEs were reported more than once in either arm. Over the duration of the study up to data cut-off, 23.6% SAEs were reported in the ruxolitinib arm *vs* 9.0% of the BAT arm. The only SAEs reported more than once were basal cell carcinoma (3 patients) and chest pain (2 patients), in the ruxolitinib arm. When corrected for exposure, the rates of SAEs for 100 patient-years were 15.3 *vs* 13.7 in the ruxolitinib *vs* the BAT arm, respectively. An overview of the Treatment-Emergent SAEs up to Week 32, regardless of the study drug relationship, is presented in Table 28.

Table 28. Serious adverse events up to Week 32, regardless of study drug relationship, by preferred term and treatment group (Safety Set – Study B2301)

	Study B2301	
	Ruxolitinib	BAT
	N= 110	N=111
Preferred term	n (%)	n (%)
Any preferred term	**15 (13.6)**	**10 (9.0)**
Acute leukemia	1 (0.9)	0
Basal cell carcinoma	1 (0.9)	0
Breast cancer	1 (0.9)	0
Bronchitis viral	1 (0.9)	0
Cardiac failure congestive	1 (0.9)	0
Cataract	1 (0.9)	0
Chest pain	1 (0.9)	0
Chronic obstructive pulmonary disease	1 (0.9)	0
Dental necrosis	1 (0.9)	0
Diverticulitis	1 (0.9)	1 (0.9)
Glaucoma	1 (0.9)	0
Leukocytosis	1 (0.9)	0
Lumbar vertebral fracture	1 (0.9)	0
Muscular weakness	1 (0.9)	0
Myelofibrosis	1 (0.9)	0
Neurological symptom	1 (0.9)	0
Neutropenia	1 (0.9)	0
Pneumonia	1 (0.9)	1 (0.9)
Post procedural haemorrhage	1 (0.9)	0
Retinal detachment	1 (0.9)	0
Splenic rupture	1 (0.9)	0
Vulvovaginitis trichomonal	1 (0.9)	0
Acute myocardial infarction	0	1 (0.9)
Atrial fibrillation	0	1 (0.9)
Bladder disorder	0	1 (0.9)
Cellulitis	0	1 (0.9)
Deep vein thrombosis	0	1 (0.9)
Fall	0	1 (0.9)
Gastroenteritis	0	1 (0.9)
Gout	0	1 (0.9)
Malignant melanoma	0	1 (0.9)
Pulmonary embolism	0	1 (0.9)
Subdural haematoma	0	1 (0.9)
Tachycardia	0	1 (0.9)

BAT= best available therapy

Over the duration of the study up to data cut-off, more SAEs were reported in the ruxolitinib arm when compared to the BAT arm, 23.6% vs 9.0%, respectively. The only SAEs reported more than once were basal cell carcinoma (3 patients) and chest pain (2 patients), in the ruxolitinib arm.

When corrected for exposure, the rates of SAEs for 100 patient-years were comparable in the two arms, 15.3 vs 13.7 in the ruxolitinib vs the BAT arm, respectively.

Deaths

There were no deaths in either of the 2 arms during the observation period (until Week 32).

In the all PV patient population 2 deaths (due to central nervous system hemorrhage and multi-organ failure, respectively) were reported within 30 days after the last dose of study drug up to data cut-off (Study B2301). The two patients were both randomized to BAT but died after crossing over to ruxolitinib. None of the deaths was suspected to be related to study drug.

Laboratory findings

An overview of abnormalities in haematology and biochemistry parameters is shown in Table 29 and Table 30, respectively.

Table 29. Newly occurring or worsening hematologic abnormalities up to Week 32 (Safety Set – Study B2301)

Test	Worsening from baseline to	Ruxolitinib N =110		BAT N=111	
		Total	n (%)	Total	n (%)
Hemoglobin (low)	Grade 1	71	35 (31.8)	80	32 (28.8)
	Grade 2	110	11 (10.0)	111	2 (1.8)
	Grade 3	110	1 (0.9)	111	0
	Grade 4	110	1 (0.9)	111	0
Leukocytes	Grade 1	107	7 (6.4)	110	10 (9.0)
	Grade 2	109	2 (1.8)	110	2 (1.8)
	Grade 3	110	1 (0.9)	111	2 (1.8)
	Grade 4	110	0	111	0
Lymphocytes	Grade 1	84	14 (12.7)	80	14 (12.6)
	Grade 2	103	16 (14.5)	101	22 (19.8)
	Grade 3	110	17 (15.5)	108	18 (16.2)
	Grade 4	110	1 (0.9)	110	2 (1.8)
Neutrophils	Grade 1	104	1 (0.9)	106	3 (2.7)
	Grade 2	106	0	108	5 (4.5)
	Grade 3	107	0	108	1 (0.9)
	Grade 4	107	1 (0.9)	108	0
Platelet (low)	Grade 1	102	20 (18.2)	99	13 (11.7)
	Grade 2	110	1 (0.9)	110	4 (3.6)
	Grade 3	110	5 (4.5)	111	3 (2.7)
	Grade 4	110	1 (0.9)	111	1 (0.9)

Total = number of patients who had missing or less than grade x at baseline and with at least one post-baseline value for the lab parameter

n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline

Patients are counted only for the worst grade observed post-baseline

New means 'grade 0' at baseline and '≥ grade 1' after baseline

BAT= best available therapy

Table 30. New or worsened biochemistry abnormalities up to Week 32 (Safety Set – Study B2301)

	Worsening from baseline to	Ruxolitinib N=110		BAT N=111	
		Total	n (%)	Total	n (%)
Alanine Aminotransferase (Hyper)	Grade 1	103	21 (19.1)	101	12 (10.8)
	Grade 2	107	3 (2.7)	109	0
	Grade 3	108	1 (0.9)	109	0
	Grade 4	108	0	109	0
Alkaline phosphatase (Hyper)	Grade 1	83	14 (12.7)	79	7 (6.3)
	Grade 2	108	1 (0.9)	108	0
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Aspartate Aminotransferase (Hyper)	Grade 1	105	21 (19.1)	101	17 (15.3)
	Grade 2	108	2 (1.8)	109	1 (0.9)
	Grade 3	108	0	109	1 (0.9)
	Grade 4	108	0	109	0

Gamma Glutamyl Transferase (Hyper)	Grade 1	95	22 (20.0)	73	14 (12.6)
	Grade 2	106	6 (5.5)	100	6 (5.4)
	Grade 3	107	4 (3.6)	109	4 (3.6)
	Grade 4	108	0	109	0
Creatinine (Hyper)	Grade 1	101	17 (15.5)	100	12 (10.8)
	Grade 2	108	1 (0.9)	109	0
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Urate (Hyper)	Grade 1	87	12 (10.9)	77	22 (19.8)
	Grade 2	101	0	97	0
	Grade 3	101	0	97	0
	Grade 4	101	2 (1.8)	97	11 (9.9)
Bicarbonate (Hypo)	Grade 1	100	30 (27.3)	97	34 (30.6)
	Grade 2	108	1 (0.9)	109	0
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Albumin (Hypo)	Grade 1	108	0	109	0
	Grade 2	108	1 (0.9)	109	1 (0.9)
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Bilirubin (Hyper)	Grade 1	97	9 (8.2)	101	9 (8.1)
	Grade 2	102	2 (1.8)	109	4 (3.6)
	Grade 3	108	2 (1.8)	109	2 (1.8)
	Grade 4	108	0	109	0
Direct Bilirubin (Hyper)	Grade 1	101	7 (6.4)	103	4 (3.6)
	Grade 2	106	2 (1.8)	109	1 (0.9)
	Grade 3	107	0	109	1 (0.9)
	Grade 4	108	0	109	0
Lipase (Hyper)	Grade 1	99	20 (18.2)	98	9 (8.1)
	Grade 2	105	6 (5.5)	108	7 (6.3)
	Grade 3	108	5 (4.5)	108	2 (1.8)
	Grade 4	108	0	109	1 (0.9)
Cholesterol (Hyper)	Grade 1	101	32 (29.1)	103	7 (6.3)

	Grade 2	107	1 (0.9)	108	0
	Grade 3	107	0	108	0
	Grade 4	107	0	108	0
Triglycerides (Hyper)	Grade 1	96	11 (10.0)	99	7 (6.3)
	Grade 2	107	0	108	0
	Grade 3	107	0	108	0
	Grade 4	107	0	108	0
Glucose (Hyper)	Grade 1	93	9 (8.2)	96	9 (8.1)
	Grade 2	103	8 (7.3)	103	7 (6.3)
	Grade 3	107	1 (0.9)	107	2 (1.8)
	Grade 4	108	0	108	1 (0.9)
Glucose (Hypo)	Grade 1	96	15 (13.6)	96	16 (14.4)
	Grade 2	104	10 (9.1)	104	9 (8.1)
	Grade 3	108	0	108	0
	Grade 4	108	0	108	0
Calcium (Hyper)	Grade 1	105	11 (10.0)	108	2 (1.8)
	Grade 2	108	0	109	1 (0.9)
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Calcium (Hypo)	Grade 1	105	15 (13.6)	106	14 (12.6)
	Grade 2	108	0	108	2 (1.8)
	Grade 3	108	2 (1.8)	109	0
	Grade 4	108	0	109	0
Phosphate (Hypo)	Grade 1	108	0	108	0
	Grade 2	108	4 (3.6)	108	2 (1.8)
	Grade 3	108	1 (0.9)	109	0
	Grade 4	108	0	109	0
Potassium (Hyper)	Grade 1	103	0	100	2 (1.8)
	Grade 2	103	13 (11.8)	100	13 (11.7)
	Grade 3	106	7 (6.4)	105	4 (3.6)
	Grade 4	108	0	109	0
Potassium (Hypo)	Grade 1	108	0	109	0
	Grade 2	108	0	109	0
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Sodium (Hyper)	Grade 1	106	2 (1.8)	107	6 (5.4)
	Grade 2	106	2 (1.8)	109	1 (0.9)
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0
Sodium (Hypo)	Grade 1	108	2 (1.8)	109	3 (2.7)
	Grade 2	108	0	109	0
	Grade 3	108	0	109	0
	Grade 4	108	0	109	0

Total = number of patients who had missing or less than grade x at baseline and with at least one post-baseline value for the lab parameter.
n = number of patients who had missing or less than grade x at baseline, and worsened to grade x post-baseline. Patients are counted only for the worst grade observed post-baseline.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Adverse events leading to study drug discontinuation up to Week 32 and data cut-off are reported in Table 31 and Table 32, respectively.

Table 31. AEs leading to study drug discontinuation up to Week 32 (SAS – Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**7 (6.4)**	**3 (2.7)**	**1 (0.9)**	**1 (0.9)**
Splenomegaly	2 (1.8)	1 (0.9)	1 (0.9)	1 (0.9)
Acute leukaemia	1 (0.9)	1 (0.9)	0	0
Dizziness	1 (0.9)	0	0	0
Leukocytosis	1 (0.9)	0	0	0
Myelofibrosis	1 (0.9)	0	0	0
Platelet count increased	1 (0.9)	1 (0.9)	0	0
Thrombocytosis	1 (0.9)	0	0	0

Preferred terms are sorted by descending frequency of ruxolitinib all grades column.
A patient could have more than one AE that led to study drug discontinuation.

Table 32. AEs leading to study drug discontinuation up to data cut-off (SAS – Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**9 (8.2)**	**5 (4.5)**	**2 (1.8)**	**1 (0.9)**
Splenomegaly	3 (2.7)	2 (1.8)	1 (0.9)	1 (0.9)
Myelofibrosis	2 (1.8)	1 (0.9)	0	0
Acute leukaemia	1 (0.9)	1 (0.9)	0	0
Dizziness	1 (0.9)	0	0	0
Hepatomegaly	1 (0.9)	0	0	0
Leukocytosis	1 (0.9)	0	0	0
Platelet count increased	1 (0.9)	1 (0.9)	0	0
Rectosigmoid cancer	1 (0.9)	1 (0.9)	0	0
Thrombocytosis	1 (0.9)	0	0	0
Arrhythmia	0	0	1 (0.9)	0

Preferred terms are sorted by descending frequency of ruxolitinib all grades column.
A patient could have more than one AE that led to study drug discontinuation
Data collected after crossover for patients randomized to BAT who crossed over to ruxolitinib are not included.

A summary of adverse events leading to dose adjustment or interruption up to data cut-off is shown in Table 33.

Table 33. Frequent AEs (at least 2% in any arm) leading to dose adjustment or interruption up to data cut-off (SAS – Study B2301)

	Ruxolitinib N=110 n (%)		BAT N=111 n (%)	
Preferred term	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Total	**51 (46.4)**	**17 (15.5)**	**17 (15.3)**	**5 (4.5)**
Anaemia	18 (16.4)	1 (0.9)	0	0
Thrombocytopenia	10 (9.1)	4 (3.6)	6 (5.4)	1 (0.9)
Pruritus	4 (3.6)	0	0	0
Dyspnea	3 (2.7)	0	0	0
Fatigue	3 (2.7)	0	0	0
Platelet count decreased	3 (2.7)	0	1 (0.9)	0

Preferred terms are sorted by descending frequency of ruxolitinib column
Of note, per protocol the patients randomized to the BAT arm could change type of BAT treatment during the study and patients who were on observation could not have a dose adjustment or interruption.
Data collected after crossover for patients randomized to BAT who crossed over to ruxolitinib are not included.

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

For the duration of the study up to data cut-off (15-Jan-2014), the mean and median duration of exposures were approximately 81 weeks in the ruxolitinib arm, and approximately 34 weeks in the BAT arm, the ratio for cumulative (patient-years) exposure of ruxolitinib to BAT was 2.33 (169.97/72.81). For crossover patients (n=96), median exposure duration was 49.6 weeks.

Discontinuation due to adverse events, regardless of causality, was observed in 3.6% of patients treated with Jakavi and 1.8% of patients treated with best available therapy (see SmPC section 4.8).

Haematological adverse reactions (any CTCAE grade) included anaemia (43.6%) and thrombocytopenia (24.5%). Anaemia or thrombocytopenia CTCAE grade 3 and 4 were reported in respectively 1.8% or 5.54%. The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%). The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). These were all CTCAE grade 1 and 2 with the exception of one CTCAE grade 3 raised alanine aminotransferase event (see SmPC section 4.8). Anaemia, thrombocytopenia, herpes zoster, dizziness, and increases of liver enzymes are already known side-effects to ruxolitinib from studies in myelofibrosis.

Through Week 32, 13.6% of the patients randomized to ruxolitinib and 9.0% in the patients randomized to BAT had at least one SAE. None of the SAEs were reported more than once in either arm. For SAEs until data cut-off, when corrected for exposure, the rates of SAEs for 100 patient-years were comparable in the two arms, 15.3 vs 13.7 in the ruxolitinib vs the BAT arm, respectively. Two deaths were reported within 30 days after the last dose of study drug up to data cut-off. None of the deaths was suspected to be related to study drug.

However there was a numerical overrepresentation of second malignancies and also of haematological transformations in the ruxolitinib arm (and also consistent with patterns in subjects subsequently crossed over to ruxolitinib). Regarding transformation/development of secondary haematological malignancies, there were numerically more transformations in the ruxolitinib arm vs. BAT up to week 32 (3 vs. 1), and 2 additional patients developed MF after crossing over to ruxolitinib. In a comparison with published data, both splenomegaly and HU resistance are associated with increased rates of hematologic transformation, 11.5-fold and 6.8-fold, respectively (Abdulkarim 2011, Alvarez- Larran 2012). Therefore, the rates of hematologic transformation in Study B2301 are lower than expected given that approximately 50% of patients in the study were HU resistant, and splenomegaly was required for eligibility.

In addition to their increased risk of haematological malignancies, PV patients are also at increased risk of non- hematologic malignancies including GI, lung, non-melanoma skin cancers, and others. The rates from the ruxolitinib studies (with a possible exception of NMSC) seem consistent with published rates in PV (12), (13),(14).

Regarding the increase in the rate of NMSCs during treatment with ruxolitinib, the list comprises 22 cases of NMSC in 10 patients. During the randomized treatment period up to the data cut-off, 8 patients treated with ruxolitinib developed NMSC compared to 2 patients treated with BAT. An imbalance in two risk factors (prior history of NMSC and mean previous exposure to HU) for NMSC between the two treatment arms may have played a possible confounding role, but the significance of these imbalances seems uncertain. Although no mechanism for a possible causal relation is known, development of NMSC is included among important potential risks in the ruxolitinib RMP. The respective warning in the SmPC has been amended (see SmPC, sections 4.4) to address the risk of the NMSCs and to recommend periodic skin examination for patients who are at increased risk for skin cancer. The MAH will also provide long-term

safety data including all second malignancies and hematologic transformations from study B2301 which is currently on-going (see risk management plan).

Preclinical information available to date suggests that from a mechanistic point of view, ruxolitinib therapy may potentially impact some cellular immune functions, involving both innate and adaptive immune responses. The clinical implications of these changes are so far unknown. The increased risk of infections, notably herpes zoster, may be one consequence of impaired immune function during ruxolitinib treatment. The MAH will continue to monitor infections as part of the important identified risk of “Infections (including Urinary Tract Infections (UTI) and Herpes Zoster; and excluding Tuberculosis)” (see Risk Management Plan).

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines (SmPC section 4.4). The MAH will continue to monitor hepatitis B cases as part of the important potential risk of “Hepatitis B reactivation” (see Risk Management Plan).

There may be an increased risk of bleeding during ruxolitinib treatment, perhaps balanced by a relative decrease in thromboembolic events. Bruising was quite common and were of grade 1-2 in the vast majority of cases. There were 13 events of GI bleeding in 9 patients, and grade 3 events accounted for 5/13. There were 2 cases of intracranial haemorrage in 2 patients. Epistaxis was seen in 13 cases, two of which were grade 3. The bleeding pattern, with preponderance for ecchymoses and mucosal bleeds, seem to resemble that in [acquired] von Willbrand disease. Possible mechanisms (eg multimer formation of vWF), including possible precautions regarding the concomitant use of platelet inhibitors otherwise recommended in MPN, will be discussed as part of the week 80 CRS of study B2301.

Patients had a median duration of exposure to Jakavi of 18.6 months (range 0.3 to 35.9 months). With longer exposure, frequency of adverse events increased; however no new safety findings emerged. When adjusted for exposure, the adverse event rates were generally comparable with those observed during the initial study period.

Recommended dose adjustments during treatment to manage decreased levels of haemoglobin and recommended starting dose for PV patients with severe renal impairment are provided in section 4.2 of the SmPC. A summary of ADRs reported in clinical studies in patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea treated with ruxolitinib as well as from post-marketing use are reported in section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

Overall, ruxolitinib is well tolerated in patients with PV with a safety profile consistent with that previously shown in patients with MF. Although no mechanism for a possible causal relation is known, development of NMSC is included among important potential risks in the ruxolitinib RMP. The MAH will continue monitoring haematological transformation (including development of MF) and secondary malignancies.

The CHMP considers the following measures necessary to address issues related to safety:

Long-term efficacy and safety of ruxolitinib including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301 should be provided. Regarding long-term effects, an interim Week 80 CSR will be available in June 2015. A final CSR will be generated when all patients will have completed the Week 208 visit or discontinued (December 2019).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list where the PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 5.0 without changes with the following content:

Safety concerns

Table 34. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppression Infections (including Urinary Tract Infection and Herpes Zoster; and excluding Tuberculosis) Tuberculosis Use in patients with hepatic impairment Use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis Elevated transaminases Bleeding (Hemorrhage) Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole Use with CYP3A4 inducers such as rifampicin
Important potential risks	Hepatitis B reactivation Progressive multifocal leukoencephalopathy AEs after discontinuation of ruxolitinib (with return of MF symptoms) Increased systolic blood pressure Developmental toxicity Non-melanoma skin cancer (NMSC) Pharmacodynamic interaction between ruxolitinib and hematopoietic growth factors or combination with cytoreductive therapies
Missing information	Safety in patients with a platelet count below 100,000/mm3 at baseline Safety in patients with an ANC <500/µL Safety in pediatric patients Risks in off-label use Long-term safety data, including secondary malignancies Safety in patients with disease severity different from those in CTs* Safety in elderly patients over 75 years of age Safety in sub-populations with genetic polymorphisms* Effect on bone marrow fibrosis*

*applicable only for MF patient population

Pharmacovigilance plan

Table 35. On-going and planned additional pharmacovigilance studies / activities in the Pharmacovigilance Plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
INCB 18424-351: (RCT, 1)	To evaluate the long-term safety of ruxolitinib in MF patients.	Myelosuppression, Infections (including UTI and herpes zoster and excluding TB), tuberculosis, Use in patients with hepatic impairment, Use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis, Elevated transaminases, bleeding, progressive multifocal leukoencephalopathy, AEs after discontinuation of ruxolitinib, Increased systolic blood pressure, Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole, Use with CYP3A4 inducers such as rifampicin, Long-term safety data, including secondary malignancies, Safety in elderly	Ongoing	Annual update: Nov-2014, Final CSR Nov-2016

		patients over 75 years of age, Effect on bone marrow fibrosis		
CINC424A2352: (RCT, 1)	To evaluate the long-term safety of ruxolitinib in MF patients	Myelosuppression, Infections (including UTI and herpes zoster and excluding TB), tuberculosis, Use in patients with hepatic impairment, Use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis, Elevated transaminases, bleeding, progressive multifocal leukoencephalopathy, AEs after discontinuation of ruxolitinib, Increased systolic blood pressure, Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole, Use with CYP3A4 inducers such as rifampicin, Long-term safety data, including secondary malignancies, Safety in elderly patients over 75 years of age, Effect on bone marrow fibrosis	Ongoing	Annual update Nov-2014 Final CSR: Nov-2015
CINC424A2201: (Randomized controlled trial [RCT], 3)	Study to evaluate the safety of ruxolitinib in MF patients with a baseline platelet	Myelosuppression, Infections (including UTI and herpes zoster and excluding TB), tuberculosis,	Ongoing	Final study report Sep-2021

	count <100,000/mm^3	Use in patients with hepatic impairment, Use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis, Elevated transaminases, bleeding, progressive multifocal leukoencephalopathy, AEs after discontinuation of ruxolitinib, Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole, Use with CYP3A4 inducers such as rifampicin, Safety in MF patients with a platelet count below 100,000/mm^3 at baseline		
CINC424AIC01T: (Observational PASS - Cohort Study, 3)	To document long-term safety of ruxolitinib in patients with myelofibrosis in a real-world setting.	Myelosuppression, Infections (including UTI and herpes zoster and excluding TB), tuberculosis, Bleeding, progressive multifocal leukoencephalopathy, AEs after discontinuation of ruxolitinib, developmental toxicity, Pharmacodynamic interaction between ruxolitinib and hematopoietic growth factors or combination with cytoreductive	Started	Final Report Jun-2019

		therapies, Long-term safety data, including secondary malignancies, Effect on bone marrow fibrosis		
CINC424B2301 Randomized controlled trial [RCT], 1	To evaluate the long-term safety of ruxolitinib in PV patients.	Long-term efficacy and safety of ruxolitinib including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301.	Ongoing	Interim (week 80 after LPLV) June 2015 Final December2019

Risk minimisation measures

Table 36. Summary table of risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Identified Risks		
Myelosuppression	SmPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warning and precautions for use): Warning, precaution for lab monitoring, dose reduction and treatment discontinuation, and description of risk factors and nature of risk. Section 4.8 (Undesirable effects) The ADRs of anaemia, thrombocytopenia and neutropenia are listed and described. Section 4.9 (Overdose) Description of nature of the risk and supportive therapy is described.	None.
Infections (including Urinary Tract Infection and Herpes Zoster; and excluding Tuberculosis)	SmPC Section 4.4 (Special warnings and precautions for use): Precaution for monitoring, treatment, and description of risk factors and nature of risk. Section 4.8 (Undesirable effects): The ADRs of urinary tract infection and herpes are described.	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Tuberculosis	SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects): The ADRs of tuberculosis are described.	None.
Use in patients with hepatic impairment	SmPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warnings and precautions for use): Instructions for starting dose and dose modifications	None.
Use in patients with moderate or severe renal failure or end stage renal failure requiring hemodialysis	SmPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warnings and precautions for use): Instructions for starting dose and dose modifications	None.
Elevated transaminases	SmPC Section 4.8 (Undesirable effects) The ADRs of raised alanine aminotransferase are listed.	None.
Bleeding (Hemorrhage)	SmPC Section 4.8 (Undesirable effects): The ADRs of bleeding events, bruising, intracranial bleeding, gastrointestinal bleeding and other bleeding events are listed and described with frequencies.	None.
Overexposure with concomitant strong CYP3A4 inhibitors or fluconazole	SmPC Section 4.2 (Posology and method of administration) Starting dose and frequent monitoring of hematological parameters Section 4.4 (Special warnings and precautions for use) Instructions for lab monitoring, starting dose and dose modifications Section 4.5 (Interactions with other medicinal products and other forms of interaction): Interactions resulting in dose reduction	None.
Use with CYP3A4 inducers such as rifampicin	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction): Information on interaction and instructions for lab monitoring, dose modifications	None.
Potential Risks		
Hepatitis B reactivation	SmPC Section 4.4 (Special warnings and precautions for use) Provides details on observations of Hepatitis B viral load elevation in patients with chronic HBV infection. Refers prescribers to clinical guidelines on monitoring and treatment of chronic HBV infection.	None.
Progressive multifocal leukoencephalopathy	SmPC Section 4.4 (Special warnings and precautions for use)	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
AEs after discontinuation of ruxolitinib (with return of MF symptoms)	SmPC Section 4.4 (Special warnings and precautions for use): Withdrawal effects Gradual tapering of the dose of ruxolitinib may be considered. Section 4.8 (Undesirable effects): The recurrence of MF symptoms is described.	None.
Increased systolic blood pressure	SmPC Section 4.8 (Undesirable effects): The ADR of increased systolic blood pressure is described.	None.
Developmental toxicity	SmPC Section 4.1 Therapeutic Indications Section 4.2 (Posology and method of administration) Section 4.3 (Contraindications) Pregnancy and lactation Section 4.6 (Fertility, pregnancy and lactation): There are no data from the use of ruxolitinib in pregnant women.	None.
Non-melanoma skin cancer	SmPC Section 4.4 (Special warnings and precautions for use)	None.
Pharmacodynamic interaction between ruxolitinib and hematopoietic growth factors or combination with cytoreductive therapies	SmPC Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction): The concurrent use of haematopoietic growth factors and Jakavi has not been studied.	None.
Missing information		
Safety in patients with a platelet count below 100,000/mm^3 at baseline	SmPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications Section 4.4 (Special warnings and precautions for use): Treatment should be discontinued in patients with platelet count less than 50,000/mm^3	None.
Safety in patients with an ANC <500/µL	SmPC Section 4.2 (Posology and method of administration): Instructions for lab monitoring, starting dose and dose modifications. Section 4.4 (Special warnings and precautions for use): Treatment should be discontinued in patients with ANC less than 500 mm^3.	None.
Safety in pediatric patients	Considering the mechanism of action of ruxolitinib it is possible that it might be used off-label in children. Prescribers are discouraged from prescribing ruxolitinib to children through the current labeling: SmPC Section 4.1 (Therapeutic indications) Section 4.2 (Posology and method of administration)	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Section 5.2 (Pharmacokinetic properties)	
Risks in off-label use	Prescribers are discouraged from prescribing ruxolitinib off-label through the current labeling: SmPC Section 4.1 (Therapeutic indications)	None.
Long-term safety data, including secondary malignancies	The safety profile of ruxolitinib is described in SmPC Section 4.8 (Undesirable effects). Currently available data do not support the need for additional risk minimization.	None.
Safety in patients with disease severity different from those in CTs*	SmPC Section 4.1 (Therapeutic indications)	None.
Safety in elderly patients over 75 years of age	SmPC Section 4.2 (Posology and method of administration): Information on dosing in elderly patients is mentioned. Currently available data do not support the need for additional risk minimization.	None.
Safety in sub-populations with genetic polymorphisms*	Currently available data do not support the need for risk minimization.	None.
Effect on bone marrow fibrosis*	Currently available data do not support the need for risk minimization.	None.

*applicable only for MF patient population

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, new warnings with regard to Hepatitis B and Non-melanoma skin cancer. The Package Leaflet has been updated accordingly. Further, Annex II has been updated to include a new post-authorisation measure; provision of long-term efficacy and safety data from Study B2301. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Jakavi. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In PV patients resistant or intolerant to HU, treatment with ruxolitinib was superior to best available therapy. Significantly more patients randomized to ruxolitinib than patients randomized to BAT met the primary endpoint (haematocrit control and at least 35% spleen volume reduction) at Week 32: 20.9% vs 0.9%, respectively ($p < 0.0001$). More patients randomized to ruxolitinib achieved haematocrit control at Week 32 when compared to patients randomized to BAT: 60.0% vs 19.6% , respectively. More patients randomized to ruxolitinib achieved at least 35% spleen volume reduction at Week 32 when compared to patients randomized to BAT: 38.2% vs 0.9% , respectively. The great majority of these responses in the ruxolitinib arm were also durable at Week 48 (among the 23 patients randomized to ruxolitinib who had achieved primary response, 22 maintained the response through data cut-off).

Furthermore, significantly more patients randomized to ruxolitinib achieved a complete haematological remission at Week 32 when compared to patients randomized to BAT: 23.6% vs 8.9%, respectively ($p=0.0028$, when adjusted for baseline platelet and WBC status).

Median spleen size, assessed by palpation, decreased from 7 cm at baseline to 1 cm at Week 32 in patients randomized to ruxolitinib, while there were no changes in patients randomized to BAT. Importantly, this was associated with a minimum of 50% reduction PV related symptoms at Week 32 in MPN-SAF TSS-14 in 48.6% in the ruxolitinib arm compared 4.9% in the BAT arm.

The data further indicated a meaningful clinical activity of ruxolitinib in PV across various subgroups constituted by subjects with more or less pronounced failure or resistance to HU. Moreover, the study population in the pivotal B2301 study appears to be reasonably representative of patients with PV resistant or intolerant to HU.

Uncertainty in the knowledge about the beneficial effects

One remaining uncertainty is the long-term results of ruxolitinib treatment. Long-term efficacy of ruxolitinib needs to be further elucidated since the potential lack of efficacy in the long term raises concern with respect to the maintenance of a positive benefit-risk balance in the applied indication Additional follow-up will further confirm the long-term effects of ruxolitinib (see discussion on clinical efficacy).

Risks

Unfavourable effects

Haematological adverse reactions included anaemia and thrombocytopenia. The three most frequent non-haematological adverse reactions were dizziness (15.5%), constipation (8.2%) and herpes zoster (6.4%). The three most frequent non-haematological laboratory abnormalities were hypercholesterolaemia (30.0%), raised alanine aminotransferase (22.7%) and raised aspartate aminotransferase (20.9%). Anaemia, thrombocytopenia, herpes zoster, dizziness, and increases of liver enzymes are already known side-effects to ruxolitinib from studies in myelofibrosis. Regarding more severe AEs and SAEs no statistical differences could be seen between ruxolitinib and BAT during the 32 comparable weeks.

Uncertainty in the knowledge about the unfavourable effects

Preclinical information available to date suggests that from a mechanistic point of view, ruxolitinib therapy may potentially impact some cellular immune functions, involving both innate and adaptive immune responses. The clinical implications of these changes are so far unknown. The increased risk of infections, notably herpes zoster, may possibly be one consequence of impaired immune function during ruxolitinib treatment. In addition, a total of six cases with a diagnosis of hepatitis B virus (HBV) reactivation while on ruxolitinib treatment have been reported to date. This has been adequately reflected in the SmPC (see section 4.4) and is reflected in the Risk Management Plan.

Evaluation of the pattern of adverse events and adverse drug reactions to ruxolitinib is somewhat complicated by the relative scarcity of comparative data (initial 32 week period of study B2301). In addition, the control arm in this case consists of a mixture of different therapies, BAT, although HU was by far the most frequently chosen BAT. The rates from the ruxolitinib studies (with a possible exception of NMSC) seem consistent with published rates in PV of second malignancies. But finding relevant comparisons is difficult and ccontinued monitoring is needed, also regarding haematological transformation (including development of MF). In regards to the risk of haematological transformation, both splenomegaly and HU resistance have been shown to be associated with increased rates of hematologic transformation, 11.5-fold and 6.8-fold, respectively. The rates of hematologic transformation in Study B2301 are lower than expected given that approximately 50% of patients in the study were HU resistant, and splenomegaly was required for eligibility. But this would not entirely remove the concern regarding the numerically higher incidence of transformations seen in the ruxolitinib arm. To address this concern, the respective warning in the SmPC has been amended (see SmPC, sections 4.4) and the MAH will also provide long-term safety data including all second malignancies and hematologic transformations from study B2301 which is currently on-going (see risk management plan).

Based on numerical but uncertain differences seen between incidences in the ruxolitinib and BAT arms, there may be an increased risk of bleeding during ruxolitinib treatment, perhaps balanced by a relative decrease in thromboembolic events. The bleeding pattern, with preponderance for ecchymoses and mucosal bleeds, seem to resemble that of von Willbrand disease. Possible mechanisms (eg multimer formation of vWF), including possible precautions regarding the concomitant use of platelet inhibitors otherwise recommended in MPN, will be discussed as part of the week 80 CRS of study B2301 which will be addressing the long-term safety of ruxolitinib in PV patients.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

In PV patients resistant or intolerant to HU, treatment with ruxolitinib was superior to best available therapy. The benefits consist of an increased control of haematocrit without phlebotomy, reduction of spleen volume, and improved control of platelet and WBC count. These improvements were supported by consistently positive PRO results in the pivotal trial B2301.

The most frequent AEs were anaemia, thrombocytopenia, dizziness, constipation and herpes zoster. The AR profile of ruxolinitib is generally manageable and is considered acceptable.

Benefit-risk balance

Ruxolitinib has a treatment effect in polycythaemia vera, and the effects is considered clinically relevant in patients who have needed treatment with a cytoreductive agent such as hydroxyurea and have

subsequently become resistant or intolerant of hydroxyurea. Therefore, in view of the manageable safety profile with the dose used in polycythaemia vera, the benefit-risk balance for ruxolitinib in the target population is positive.

Discussion on the Benefit-Risk Balance

In patients with PV failing HU therapy, there are currently no well-established treatment options. The demonstrated effects of ruxolitinib in PV are considered clinically relevant in patients who have needed treatment with a cytoreductive agent such as hydroxyurea and have subsequently become resistant or intolerant of hydroxyurea. Available data indicated a meaningful clinical activity of ruxolitinib in PV across various subgroups constituted by subjects with more or less pronounced failure or resistance to HU, with an acceptable adverse effects profile. In younger patients with "minimal" resistance to HU, remaining uncertainties about long term side effects need particular consideration. Long-term efficacy of ruxolitinib needs to be further elucidated since the potential lack of efficacy in the long term raises concern with respect to the maintenance of a positive benefit-risk balance in the applied indication.

The CHMP considers the following measure necessary to address the issues related to efficacy and safety:

Post-Authorisation Efficacy Study to provide long-term efficacy and safety of ruxolitinib including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to add treatment of adult patients with polycythaemia vera resistant to or intolerant of hydroxyurea based on the results of Study B2301 (RESPONSE). As a result, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, Annex II has been updated to include a new post-authorisation measure; provision of long-term efficacy and safety data from Study B2301. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. Further, an updated RMP version 5.0 was approved as part of the application.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following new condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
• Post-Authorisation Efficacy Study to provide long-term efficacy and safety of ruxolitinib data including (late) achievement of response, duration of (various) responses, as well as incidence of AEs including haematological transformation and second malignancies from the study B2301.	Week 80 CSR: June 2015 Final CSR: December 2019

REFERENCES

1. Borchmann P, Treml JF, Hansen H, Gottstein C, Schnell R, Staak O, et al. The human anti-CD30 antibody 5F11 shows in vitro and in vivo activity against malignant lymphoma. Blood. 2003;102(10):3737-42. Epub 2003/07/26. doi: 10.1182/blood-2003-02-0515. PubMed PMID: 12881320.

2. Spivak JL, Considine M, Williams DM, Talbot CC, Jr., Rogers O, Moliterno AR, et al. Two clinical phenotypes in polycythemia vera. The New England journal of medicine. 2014;371(9):808-17. Epub 2014/08/28. doi: 10.1056/NEJMoa1403141. PubMed PMID: 25162887; PubMed Central PMCID: PMC4211877.

3. Johansson P. Epidemiology of the myeloproliferative disorders polycythemia vera and essential thrombocythemia. Seminars in thrombosis and hemostasis. 2006;32(3):171-3. Epub 2006/05/05. doi: 10.1055/s-2006-939430. PubMed PMID: 16673273.

4. Finazzi G, Barbui T. Evidence and expertise in the management of polycythemia vera and essential thrombocythemia. Leukemia. 2008;22(8):1494-502. Epub 2008/07/04. doi: 10.1038/leu.2008.177. PubMed PMID: 18596737.

5. Marchioli R, Finazzi G, Specchia G, Cacciola R, Cavazzina R, Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. The New England journal of medicine. 2013;368(1):22-33. Epub 2012/12/12. doi: 10.1056/NEJMoa1208500. PubMed PMID: 23216616.

6. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood. 2007;109(6):2446-52. Epub 2006/11/16. doi: 10.1182/blood-2006-08-042515. PubMed PMID: 17105814.

7. Tibes R, Mesa RA. Emerging drugs for polycythemia vera. Expert opinion on emerging drugs. 2013;18(3):393-404. Epub 2013/08/24. doi: 10.1517/14728214.2013.832754. PubMed PMID: 23968379.

8. Passamonti F. How I treat polycythemia vera. Blood. 2012;120(2):275-84. Epub 2012/05/23. doi: 10.1182/blood-2012-02-366054. PubMed PMID: 22611155.

9. Antonioli E, Guglielmelli P, Pieri L, Finazzi M, Rumi E, Martinelli V, et al. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. American journal of hematology. 2012;87(5):552-4. Epub 2012/04/05. doi: 10.1002/ajh.23160. PubMed PMID: 22473827.

10. Verner E, Forsyth C, Grigg A. Cyclical thrombocytosis, acquired von Willebrand syndrome and aggressive non-melanoma skin cancers are common in patients with Philadelphia-negative myeloproliferative neoplasms treated with hydroxyurea. Leukemia & lymphoma. 2014;55(5):1139-43. Epub 2013/07/25. doi: 10.3109/10428194.2013.827788. PubMed PMID: 23879199.

11. Geyer HL, Mesa RA. Therapy for myeloproliferative neoplasms: when, which agent and how? Blood. 2014. Epub 2014/12/05. doi: 10.1182/blood-2014-05-577635. PubMed PMID: 25472969.

12. Frederiksen H, Farkas DK, Christiansen CF, Hasselbalch HC, Sorensen HT. Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study. Blood. 2011;118(25):6515-20. Epub 2011/11/01. doi: 10.1182/blood-2011-04-348755. PubMed PMID: 22039256.

13. Alvarez-Larran A, Pereira A, Cervantes F, Arellano-Rodrigo E, Hernandez-Boluda JC, Ferrer-Marin F, et al. Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera. Blood. 2012;119(6):1363-9. Epub 2011/12/14. doi: 10.1182/blood-2011-10-387787. PubMed PMID: 22160617.

14. Marchioli R, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(10):2224-32. Epub 2005/02/16. doi: 10.1200/JCO.2005.07.062. PubMed PMID: 15710945.