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Redacted Protocol

Oncology Clinical Development & Medical Affairs

INC424 – Ruxolitinib, Jakavi

Post Authorization Safety Study CINC424AIC01T

A Non-Interventional Long-term Safety Study of Ruxolitinib in Myelofibrosis

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Medicinal product	Jakavi
Product reference	Jakavi
Procedure number	EMEA/H/C/2464
Marketing authorization holder(s)	Novartis Pharma A.G. Lichtstrasse 35, 4056 Basel,Switzerland
Joint PASS	No

Research questions and objectives	This non-interventional, observational study will provide real-world safety data on MF patients exposed and non-exposed to ruxolitinib and therefore provide insights into disease management as well as the safety profile of ruxolitinib. This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union. The primary objective of this Post Authorization Safety Study is to document long-term safety of ruxolitinib in patients with myelofibrosis in a real-world setting according to the current prescribing information of the European label. The secondary objectives are to document the treatment of patients with MF including pharmacological and non-pharmacological management and To document the incidence and outcome of events of special interest including the following: • bleeding events • serious & opportunistic infections • secondary malignancies • ADRs/ SAEs after discontinuation of ruxolitinib treatment • Pregnancies • deaths of any cause
Countries of study	Austria, France, Germany, Italy, Netherlands, Switzerland, UK
Authors	[redacted]

[redacted]

Marketing authorization holder(s)

Marketing authorization holder	Novartis Pharma A.G. Lichtstrasse 35, 4056 Basel, Switzerland
MAH contact person	[redacted]

1 Table of contents

List of tables

List of figures

2 List of abbreviations

AE	Adverse Events
ADR	Adverse Drug Reaction
AML	Acute Myeloid Leukemia
ATC	Anatomical Therapeutical Chemical Classification System,
COMFORT	Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment
CPO	Country Pharma Organization
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
DMC	Data Monitoring Committee
DS&E	Drug safety and epidemiology
EC	Ethics Committee
EAP	Expanded Access Program
eCRF	electronic Case Report/Record Form
ELN	European Leukemia Network
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERNEST	European Registry for Myeloproliferative Neoplasms towards a better understanding of Epidemiology, Survival and Treatment
ESA	Erythropoiesis Stimulating Agent
ET	Essential thrombocythemia
EUMNET	European Myelofibrosis Network
FAS	Full analysis set
FPFV	First patient first visit
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GPP	Good Pharmacoepidemiological Practice
Hgb	Hemoglobin
HU	Hydroxyurea
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
IMID	Immunomodulatory Drugs
IPSS	International Prognostic Scoring System
IPSP	Individual Patient Supply Program
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus kinase
LPFV	Last patient first visit
LPLV	Last patient last visit
MAA	Marketing Authorization Application

MedDRA	Medical dictionary for regulatory activities
MF	Myelofibrosis
MPN	Myeloproliferative neoplasms
NIS	Non-interventional Study
PASS	Post-Authorization Safety Study
PET-MF	Post essential thrombocythemia-myelofibrosis
PI	Principal Investigator
PMF	Primary myelofibrosis
PPV-MF	Post polycythemia vera-myelofibrosis
PSUR	Periodic Safety Update Report
PRBC	Packed Red Blood Cells
PV	Polycythemia vera
QoL	Quality of life
REB	Research Ethics Board
SAE	Serious Adverse Event
SCT	Stem cell transplant
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
ULN	Upper limit of normal
UTI	Urinary tract infection
WHO	World Health Organization
WBC	White blood cell count

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4 Abstract

Title	Non Interventional Ruxolitinib in Myelofibrosis Long term Safety Study
Version and Date	Version 01 11 April 2014
Name and affiliation of main author	[redacted]
Rationale and background	Myelofibrosis, an orphan condition, is a myeloproliferative neoplasm characterized by progressive anemia, leucopenia or leucocytosis, thrombocytopenia or thrombocythemia, profound remodeling of bone marrow architecture with fibrosis, and multiorgan extramedullary hematopoiesis, which primarily involves the liver and spleen. Ruxolitinib is a first-in-class oral JAK 1/JAK 2 inhibitor studied for the treatment of myelofibrosis. There were two Phase III pivotal studies: COMFORT-I (Verstovsek et al. 2012), a placebo controlled study of 309 patients, randomized 1:1, conducted in the US, Canada, and Australia under FDA Special Protocol Assessment, and COMFORT-II conducted by Novartis (Harrison et al 2012), an open-label study of 219 patients, randomized 2:1 between ruxolitinib and BAT, conducted in nine European countries under CHMP Scientific Advice. The primary endpoint of these studies based on standard response criteria for spleen length in MF is the proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at week 24 in COMFORT I, and at week 48 in COMFORT II, as measured by MRI or CT scan. Both Phase III studies met their primary endpoint of 35% reduction in spleen volume. Thrombocytopenia and anemia were predictable and manageable with dose modifications. Bleeding, most frequently presenting as bruising has been identified as a risk associated with ruxolitinib treatment, mainly in the context of thrombocytopenia. Other identified risks of are infections, although confounded by the immunocompromization due to the underlying condition. The data from the two Phase III study led to the subsequent registration of ruxolitinib with the health authorities both in the US and EU. Although the number of patients exposed in clinical studies is significant considering orphan status of MF, the experience is limited by the absence of post- marketing exposure including data on long term use, and the typical restrictions imposed by inclusion and exclusion criteria in clinical studies. Therefore it was agreed with the health authorities of the EMA to collect data from patients with myelofibrosis treated with ruxolitinib or with other treatments outside of clinical trial in normal clinical practice as a post- authorization safety study (PASS)
Research question and objectives	This non-interventional, observational study will provide real-world safety data on MF patients exposed and non-exposed to ruxolitinib and therefore provide insights into disease management as well as the safety profile of ruxolitinib. This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union Primary objective The primary objective of this Post Authorization Safety Study is to document long-term safety of ruxolitinib in patients with myelofibrosis in a real-world setting according to the current prescribing information of the European label.

	Secondary objectives To document the treatment of patients with MF including pharmacological and non-pharmacological management. To document the incidence and outcome of events of special interest including the following: • bleeding events • serious & opportunistic infections • secondary malignancies • deaths of any cause
Study design	This Post Authorization Safety Study is planned as a prospective, multi-center, multi-national non-interventional study for patients diagnosed with myelofibrosis
Population	Adult patients with a diagnosis of primary or secondary myelofibrosis Inclusion criteria Patients diagnosed with primary Myelofibrosis according to WHO criteria and secondary Myelofibrosis (Post- PV MF and Post –ET MF) according to IWG-MRT (International Working Group for Myelofibrosis Research and Treatment) criteria. Exclusion criteria Patients not providing informed consent Patients participating concurrently in an investigational study involving ruxolitinib or another JAK inhibitor. Note: patients previously treated with ruxolitinib through the Individual Patient Supply Program (IPSP) or enrolled in the Expanded Access Study CINC424A2401 (JUMP) and switched to commercial drug supply are eligible.
Variables	This study is observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data will be collected at patients' visits to their site. To maintain adequate data collection, the sites will be encouraged to provide any updated patient data at 3-monthly intervals.
Data sources	The data for this study will be retrieved from Oracle Clinical/Remote Data Capture 4.6.2 A designated Contract Research Organization (CRO) will perform the analysis following their own internal Standard Operating Procedures (SOPs) that have been reviewed and approved by Novartis. Sites enrolling patients in this study will record data on eCRF provided by Novartis (or designee) which will capture, check, store and analyze the data. CRO will follow their own internal SOPs that have been reviewed and approved by Novartis. Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
Study size	The study is planned to recruit patients diagnosed with MF exposed and non-exposed to ruxolitinib with the objective of enrolling at least 300 patients exposed to ruxolitinib within 2 years. [redacted]. Total number of ruxolitinib exposed MF patients: 300 Total number MF patients non-exposed to ruxolitinib 150 (estimate) Number of sites: 100 (estimate) Number of patients per site: 3-5 Location of sites: European Union
Data analysis	Demographic and other baseline characteristics including medical history and prior treatment will be summarized descriptively. The incidence of on- treatment adverse events will be summarized by system organ class and preferred term using the MedDRA dictionary. Similar summaries will also be produced for treatment-related adverse events. All ADR and SAE data will be analyzed for identified and potential risks as presented in the RMP

	Sample size calculation: With 300 patients, there is 95% probability that at least 1 patient will experience an adverse event that has a true probability of occurrence of 1%. Furthermore, 300 patients will provide enough precision to ensure the margin of error on a 95% confidence interval for estimating the rate of specific AEs of interest (herpes zoster, UTI, tuberculosis, bleeding, and intracranial hemorrhage) is less than 5%, assuming the observed rate is similar to what was observed in the prior phase III studies.
Milestones	[redacted]

5 Amendment and updates

Changes to the specific sections of the protocol are shown in the track changes version of the protocol using red strikethrough for deletions, red underline for insertions, green double strikethrough for "moved from", green double underline for "moved to", light blue for inserted cells and pink for deleted cells.

Table 5-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
01	12-Jun-2014	Entire protocol	The content of the original version has been reported consistently with the new template structure	To adapt the original protocol to the new Novartis template for non-interventional studies
		Cover page	Author's list has been revised and new authors added	Update the author's list
		Original version: Synopsis (Objectives) Version 01: Section 4 (Research question and objectives)	The bullet points: "ADRs/SAEs" and "pregnancies" have been deleted	To correct the list of the events of special interest and make it consistent with the list reported in the protocol
		Original version: Synopsis	The following paragraphs: • Dose regimen • treatment cycle • supply, preparation administration • special safety assessments have been deleted because not foreseen in the new template	To adapt the original protocol to the new Novartis template for non-interventional studies
		Original version: Synopsis (key milestones)	The following date: [redacted] has been changed as follows:	To update the protocol milestones according to the new timelines

Number	Date	Section of study protocol	Amendment or update	Reason
		Version 01: section 4 (milestones)	[redacted]	
		Version 01: Section 4	Countries involved added	To adapt the original protocol to the new Novartis template for non-interventional studies
		Original version: Section3.1 Version 01: Table 6.1 and section 9.1	FPFV actual date has been inserted and the following timelines: [redacted]	To update the timelines
		Original version: Section3.1 Version 01: Table 6.1 and Section 9.1	FPFV actual date inserted	To update the timelines
		Original version: synopsis and Section 3.2.1 Version 01: Section 4 and Section 9.2.2	Inclusion criterion: reference to IWG-MRT criteria for diagnosis of secondary Myelofibrosis has been inserted	To clarify the diagnostic criteria used to enroll secondary MF patients
		List of abbreviations	New terms inserted	To adapt the list to the new Novartis template for non-interventional studies
		Original version: Section 3.3.4 Version 01: Section: 9.3.4	The term ”Event of special interest” has been inserted in this paragraph	To update the sentence
		Version 01: Section 9.4	The new paragraph: “data sources” has been inserted	To adapt the original protocol to the new Novartis template for non-interventional studies

Number	Date	Section of study protocol	Amendment or update	Reason
		Original version: Section 4.3 Version 01: Section: 9.6.3	The sentence: “the data are de-identified and moved from the database maintainer to the analysis database of the sponsor” has been corrected as follows: ”the data will be moved to the analysis data set”	To clarify the data transfer procedure
		Original version: Table 5.1 Version 01: Table 9.1	UTI has been deleted and tuberculosis has been inserted	To correct the table footer
		Version 01: Section 9.8	The new paragraph: “quality control” has been inserted	To adapt the original protocol to the new Novartis template for non-interventional studies
		Original version: section Figure 6-1 Version 01: Figure 12.1	The sentence: “periodic transfer of data collected in CINC424AIC01T and required in the ELN ERNEST disease registry“ has been corrected deleting “periodic” and inserting “cleaned”	To correct the sentence on data transfer
		Version 01: Annex 2	The ENCePP check list has been added	To adapt the original protocol to the new Novartis template for non-interventional studies

6 Milestones

[redacted]

[redacted]	[redacted]
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7 Rationale and background

Myelofibrosis (MF) is a myeloproliferative neoplasm. The condition of interest includes all types of MF, i.e., primary myelofibrosis (PMF), and secondary myelofibrosis: post-polycythemia vera MF (PPV-MF) or post-essential thrombocythemia MF (PET-MF). The 10-year risk of developing MF is < 4% in ET and 10% in PV. The median age at diagnosis is approximately 65 years (Barbui et al. 2011). The incidence of PMF has been shown to increase with age and is estimated at 0.4 to 1.4 cases per 100,000 individuals per year in Western countries. The condition fulfills the criteria of an orphan disease.

Patients with PMF, PPV-MF, or PET-MF have a critical unmet medical need. MF patients suffer from debilitating symptoms and often massive splenomegaly (Barbui et al. 2011, Mesa et al. 2007). None of the previously available drugs used to treat MF was approved for use in this indication in the United States until the approval of ruxolitinib in November 2011. In the EU, HU is approved on a national basis in a few countries (e.g. France, Italy, Sweden and Spain) and is used to control excessive myeloproliferation. Other therapeutic options include splenectomy, splenic irradiation and the potentially curative option of allogeneic stem cell transplant (Ciurea et al. 2008; Bacigalupo et al. 2010). Splenectomy has been reported to result in perioperative complications in 31% and death in 9% of patients.

The disease is known to be associated with dysregulated JAK1 and JAK2 signaling. These mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms.

MF can present as an apparently de novo disorder (PMF) or evolve from other MPNs, and can be termed secondary MF, PPV-MF or PET-MF (Mesa et al. 2007; Barbui et al. 2011). The hallmark feature of MF is massive splenomegaly. The clinical presentation of the disease is also characterized by progressive anemia, leucopenia or leucocytosis, thrombocytopenia or thrombocythemia, profound remodeling of bone marrow architecture with fibrosis, and multiorgan extramedullary hematopoiesis, which primarily involves the liver and spleen (Mesa et al. 2007; Barbui et al. 2011). Patients may experience severe constitutional symptoms, sequelae of massive splenomegaly (portal hypertension, hepatic obstruction and splenic infarction), dyspnea, pain, limited mobility, early satiety, a catabolic state with cachexia, ineffective hematopoiesis and hematopoietic failure, risk of vascular events (including thrombosis and hemorrhage), progression to leukemia, and premature death. Causes of death for patients with MF include leukemic transformation, infections, bleeding, thrombosis, heart failure, liver failure, solid tumors, respiratory failure, and portal hypertension (Cervantes et al. 2009).

A retrospective multicenter analysis reported by (Cervantes et al. 2009) on behalf of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) identified 5 risk factors independently associated with shortened survival in PMF: age > 65 years, presence of constitutional symptoms (weight loss, fever, or night sweats), anemia as determined by hemoglobin (Hgb) < 10 g/dL, leukocytosis (white blood cell [WBC] count > 25 x 10^9/L), and a circulating blast percentage of ≥ 1%. This scoring system is termed the International Prognostic Scoring System (IPSS). The IWG-MRT identified 4 risk groups with non-overlapping survival curves based on the absence or presence of 1 or more of these risk factors. The median survival of patients was 135 months in the Low risk group (zero risk factors), 95 months in the Intermediate-1 risk group (1 risk factor), 48 months in the Intermediate-2 risk group (2 risk factors), and 27 months in the High risk group (≥ 3 risk factors) . Analysis of relative survival showed that mortality in all of the patients at 5 and 10 years after diagnosis was 40% and 60% greater, respectively, than the expected mortality in a general population with similar demographic characteristics. Further study of the IPSS has resulted in the development of two additional scoring systems to assess the prognostic value of risk factors emerging after patients are diagnosed with PMF: the Dynamic International Prognostic Scoring System (DIPSS) which increases the relative importance of the presence of anemia in the prognostic model in proportion to its greater association with decreased survival (Passamonti et al. 2010); and the DIPSS Plus, a refined scoring system that additionally accounts for karyotype, platelet count, and transfusion status information (Verstovsek et al. 2010).

Patients with PMF, PPV-MF, or PET MF have a critical unmet medical need. Hydroxyurea as well as other therapies commonly used to treat MF (erythropoietic-stimulating agents, androgens and steroids) have been evaluated in small series of patients, and never in a randomized, controlled Phase III study. Other drugs including busulfan, melphalan, and 2-chlorodeoxyadenosine have been used to treat patients refractory to HU, but have had little or no effect on the disease. Few patients treated with these agents experience broad or durable clinically meaningful improvement in their symptoms and tolerability is variable. Splenectomy has been reported to result in perioperative complications in 31% and death in 9% of patients. Although splenic irradiation has been associated with reductions in spleen size in 80-95% of cases and relief in abdominal discomfort in up to 100% of the patients for a median of six months, it is associated with significant and prolonged myelosuppression with a mortality rate as high as 13%. The only potentially curative therapy for MF remains allogeneic stem cell transplantation (alloSCT). However, not only is donor availability a limiting factor, but the 1-year transplant-related mortality in patients who undergo alloSCT is 27%, and alloSCT is rarely a viable option in patients > 60 years of age (Bacigalupo et al. 2010; Ciurea et al. 2008). In the review of the DIPSS only 8 of 525 patients (1.5%) had undergone an alloSCT, demonstrating the rarity of this therapeutic option for most MF patients. Overall, the low success rate of existing therapeutic interventions used to treat MF attests to a substantial medical need.

There were two Phase III pivotal studies: COMFORT-I (Verstovsek et al. 2012), a placebo controlled study of 309 patients, randomized 1:1, conducted in the US, Canada, and Australia under FDA Special Protocol Assessment, and COMFORT-II conducted by Novartis (Harrison et al. 2012), an open-label study of 219 patients, randomized 2:1 between ruxolitinib and BAT, conducted in nine European countries under CHMP Scientific Advice. The primary endpoint of these studies based on standard response criteria for spleen length in MF is the proportion of patients achieving ≥ 35% reduction in spleen volume from baseline at week 24 in COMFORT I, and at week 48 in COMFORT II, as measured by MRI or CT scan. This volumetric reduction corresponds with the European Myelofibrosis Network (EUMNET) and IWG-MRT definitions of Clinical Improvement. Secondary endpoints include durability of spleen response, symptomatic improvement, as well as leukemia-free survival and overall survival. Both Phase III studies met their primary endpoint of 35% reduction in spleen volume.

The analysis of survival data from both trials did demonstrate a survival advantage for patients treated with ruxolitinib in the COMFORT I-trial (Verstovsek et al. 2012). However no benefit of ruxolitinib on survival was yet observed in the COMFORT II study (Harrison et al 2012), and the authors argue that this analysis may be confounded by the high crossover rate from best available therapy of 25% and withdrawal without follow-up of another 12% of the patients.

Grade 3-4 laboratory findings of anemia and thrombocytopenia were reported with ruxolitinib at rates of 38.3% and 8.3%, respectively, compared with 20.6% and 6.8% on BAT (COMFORT-II); and with ruxolitinib at rates of 45.2% and 12.9%, respectively, compared with 19.2% and 1.3% on Placebo (COMFORT-I). Thrombocytopenia and anemia were predictable and manageable with dose modifications. Bleeding, most frequently presenting as bruising has been identified as a risk associated with ruxolitinib treatment, mainly in the context of thrombocytopenia. Other identified risks of are infections, although confounded by the immunocompromization due to the underlying condition. Areas of special interest for the collection of drug usage safety data are drug exposed pregnancies and the development of secondary malignancies.

In the US, ruxolitinib was first licensed and marketed in 2011 indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. At the time point of submission of the Marketing Authorization Application in the EU, a total of 589 MF patients were exposed to ruxolitinib phase 3 studies, which was equivalent to 622 patient years of exposure. Although the number of patients exposed in clinical studies is significant considering orphan status of MF, the experience is limited by the absence of post marketing exposure including data on long term use and the typical restrictions imposed by inclusion and exclusion criteria in clinical studies. This study will provide real-world data on MF patients exposed and non-exposed to ruxolitinib and will therefore provide insights into disease management as well as the safety profile of ruxolitinib.

8 Research question and objectives

This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union.

Primary objective

The primary objective of this Post Authorization Safety Study is to document long-term safety in patients with myelofibrosis prescribed ruxolitinib according to the prescribing information.

Secondary objectives

1. To document the treatment of patients with MF including pharmacological and non-pharmacological management.
2. To document the incidence and outcome of events of special interest including the following:
   - bleeding events
   - serious & opportunistic infections
   - secondary malignancies
   - ADRs/ SAEs after discontinuation of ruxolitinib treatment
   - pregnancies
   - deaths of any cause

9 Research methods

9.1 Study design

This is a Post Authorization Safety Study according to the EU Volume 9a of the Rules Governing Medicinal Products in the European Union and is planned as a prospective, multi-center, multi-national disease registry for patients diagnosed with myelofibrosis. The study is planned to recruit patients diagnosed with MF exposed and non-exposed to ruxolitinib with the objective of enrolling at least 300 patients exposed to ruxolitinib within 2 years. It is expected that about 150 patients not exposed to ruxolitinib will be recruited during the enrolment period. [redacted]

Participating sites will be identified in collaboration with European Leukemia Net (ELN, an academic network of excellence dedicated to improve the treatment of patients with hematologic malignancies) . To allow the recruitment of 300 patients, it is expected that 100 sites will be participating in this MF disease registry.

9.1.1 Visit schedule and assessments

This study is non-interventional or observational in nature and does not impose a therapy protocol, diagnostic/therapeutic interventions or a visit schedule. Available data from routine clinical management of the patients will be collected at patients' visits to their site. To maintain adequate data collection, the sites will be encouraged to provide any updated patient data at 3-monthly intervals.

9.1.2 Discussion of study design and feasibility

To date, no large prospective observational studies have been reported that provide insight into current treatment patterns or detailed information on disease associated conditions and outcomes.

The chosen design will allow collection of data on all patients with a confirmed diagnosis of MF, irrespective of treatment modalities employed, disease severity, age, concurrent conditions or other factors that are typically controlled in interventional settings by inclusion- or exclusion criteria. Data on drug exposure including ruxolitinib, the emergence and management of events of special interest, the use of combination drug therapies, and the outcome of pregnancies will be made available. In addition, the non-interventional study logistics allow the collection and transmission of SAE and ADR data collected for patients exposed to ruxolitinib.

Ruxolitinib as an innovative treatment is intended for the long term treatment of MF. The design and logistics of the non-interventional study will allow a follow-up of "real-world" patients for 3 to 5 years. This is significantly longer than exposure experience from ruxolitinib clinical studies in MF patients. Furthermore, the disease registry will allow the continued follow-up of patients independent of exposure to certain drugs. The study will collect data from several European countries. This may balance for local treatment patterns.

There are several limitations to the study: a direct comparison or hypothesis testing between patients exposed to ruxolitinib and those who are not will not be possible due to confounding factors; i.e., patients with few manifestations of MF are expected to be managed differently from those with a more serious manifestations such as massive splenomegaly and pronounced disease symptoms. Still, data received on non-exposed patients will provide valuable context information that support the interpretation of observations made. Potential or identified risks related to ruxolitinib drug treatment have been characterized and quantified in (interventional) phase III clinical studies and therefore represent an important reference. It will therefore be possible to review solicited safety observations from this non-interventional study in the context of the safety profile of ruxolitinib established from MF clinical studies.

This Post Authorization Safety Study is aiming to collect comprehensive data on the evolution and management of the condition rather than on isolated parameters. The primary objective is to collect *long-term* safety data for ruxolitinib exposed patients. Therefore, for selection of participating sites several aspects were reviewed:

Firstly, participating centers have to be qualified for the treatment and management of patients with hematologic malignancies and have the infrastructure for adequate data management according to GCP, including back-up of trained personnel. Secondly, to reduce missing data or loss to follow-up centers should offer, ideally within the same institution, medical services from other disciplines that are required for the management of MF complications or MF treatment escalation.

Major academic centers organized within the ELN were therefore contacted and requested to provide an estimate of the number of patients diagnosed with MF. Data from ELN centers indicated 10-20 patients with MF are currently managed per site, whereas it is expected by the experts that eligible mid-size sites currently manage 3-5 patients. It was assumed that 85% of MF patients at a site will provide informed consent for the data collection in the disease registry.

Based on above information and assumptions, and considering the participation of 15 large sites the recruitment of 300 MF patients exposed to ruxolitinib in the registry within 2 years, it is estimated that 100 centers will be required to reach the recruitment target. A total of 100 suitable centers were identified in collaboration with the ELN in EU countries.

The recruitment of patients will be monitored on a continuous basis by Novartis. If the recruitment rate falls below projections, Novartis will make any effort to identify and qualify additional sites. The identification of additional sites will be performed with involvement of the ELN, for which the ERNEST registry will provide information on potential candidates.

9.2 Setting

9.2.1 Patient population

Adult patients with a diagnosis of primary or secondary Myelofibrosis

9.2.2 Inclusion and exclusion criteria

Inclusion criteria

- Patients diagnosed with primary Myelofibrosis according to WHO criteria and secondary Myelofibrosis (Post- PV MF and Post –ET MF) according to IWG-MRT (International Working Group for Myelofibrosis Research and Treatment) criteria.

Exclusion criteria

- Patients not providing informed consent
- Patients participating in an investigational study involving ruxolitinib or another JAK inhibitor

Note: patients previously treated with ruxolitinib through the Individual Patient Supply Program (IPSP) or enrolled in the Expanded Access Study CINC424A2401 and switched to commercial drug supply are eligible.

9.3 Variables

9.3.1 General considerations for data collection

With respect to the observational or non-interventional nature of the PASS, only examinations may be recorded if they are part of the routine assessment of the patients. No examinations should be conducted for the purpose of completing this protocol alone, as this would change the study to interventional.

However every effort should be made to carefully collect and record all available data for safety, treatment, and treatment outcome of the individual patient enrolled in this PASS, and to complete the case report form (CRF) as comprehensive as possible.

9.3.2 Baseline disease characteristics and demographics

Unless otherwise stated, *baseline* is defined as the first observation at the time the patient is included in the registry. The following information will be collected at baseline:

1. Patient age, gender and race
2. MF diagnosis (major and minor criteria which qualified the patient for diagnosis of MF)
3. Date of first diagnosis of MF
4. MF current risk group (DIPSS risk category for patients previously diagnosed and IPSS risk category for newly-diagnosed)
5. JAK2V617F mutation status
6. Spleen Length
7. Constitutional Symptoms
8. Body weight
9. Prior transfusional history (PRBC's and platelets)
10. Date and results of bone-marrow biopsies (including fibrosis score and staining methodology)
11. Prior treatments of MF, including dose, dates and duration (whichever data are available), including interventions such as splenectomy or irradiation therapy
12. Co-morbidities, including organ impairments and previous infections
13. Prior history of malignancies with date of first diagnosis, pathology, treatments and current state

9.3.3 Management of myelofibrosis and co-morbidities

During the observation period the following information on the management of MF will be collected:

1. Medications for treatment and management of MF (e.g. ruxolitinib, HU, IMIDs, Peg Interferon, Danazol, ESA) with start date, stop date, dose and dose change, and reason for dose change or discontinuation, as appropriate
2. Non-pharmacologic treatments for MF (splenic irradiation, splenectomy, BMT) including dates, morbidities, duration of response and outcome
3. Medications for MF symptoms, with start and stop date, dose and indication
4. Use of blood or platelet transfusions
5. Medications for the management of co-morbidities, with start and stop date, dose and indication
6. Subsequent bone marrow biopsies as clinically indicated during standard clinical care, reporting fibrosis scores and blast percentage
7. Spleen length
8. Constitutional symptoms
9. Body weight
10. JAK2V617F allele burden measurements, chromosomal abnormalities

9.3.4 Laboratory evaluations

At baseline and during the observation period laboratory data will be collected and recorded by their respective CTCAE category Version 4 grades:

1. Hematology
2. Clinical chemistry

Other relevant laboratory abnormalities that represent an Adverse Reaction an Event of Special Interest or a Serious Adverse Event will be collected. This includes laboratory values that are required for the interpretation of Adverse Reactions. Events of Special Interest and Serious Adverse events.

9.3.5 Treatment discontinuation

Reason(s) of discontinuation of patients from the non-interventional study will be collected:

- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death

9.4 Data sources

The data for this study will be retrieved from the Oracle Clinical /Remote Data Capture 4.6.2 provided by Novartis or designee. A designated contract research organization (CRO) will perform the analysis following their own internal standard operating procedures (SOPs) that have been reviewed and approved by Novartis.

Initiation of the participating sites will be performed by Novartis and/or a designated CRO. Before study initiation, a Novartis representative (or designee) will review the protocol and CRF with the physicians and their staff.

Sites enrolling patients in this study will record data on eCRFs provided by Novartis (or designee) which will capture, check, store and analyze the data.

CROs will follow their own internal SOPs that have been reviewed and approved by Novartis.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data will be transferred to Novartis at a frequency as defined in the protocol. Clinical data will be transferred to Novartis after closure of the study.

Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete if possible at every patient visit the appropriate CRF.

However, the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most patients being treated with ruxolitinib is at 3-monthly intervals.

For patients who discontinue prematurely, the reason for discontinuation should be determined.

9.5 Study size

The study is planned to recruit patients diagnosed with MF exposed and non-exposed to ruxolitinib with the objective of enrolling at least 300 patients exposed to ruxolitinib within 2 years. It is expected that about 150 patients not exposed to ruxolitinib will be recruited during the enrolment period.

9.6 Data management

9.6.1 Monitoring Procedures

Before study initiation the sponsor personnel or a designated representative will review the protocol and corresponding documents with the investigators and their staff. During this study a field monitor may visit the site to check the completeness of patient records, the accuracy of entries in the database, the adherence to the protocol and to GCP. Key study personnel must be available to assist the field monitor during these visits. The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the entries in the database. No information in these records about the identity of the subjects will leave the study center. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of serious adverse events and the recording of primary variables if available. Additional checks of the consistency of the source data with the data entered in the database are performed according to the study-specific monitoring plan.

9.6.2 Data collection

The investigator must complete the data entry forms in the database. All entries to the data forms must be made as described in completion guidelines or as instructed by the sponsor personnel or the designated representative at study initiation. Data on subjects collected during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the sponsor and the investigator are bound to keep this information confidential. The investigator must maintain source documents for each patient in this study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc., and keep a copy of the signed informed consent form. All information on data report forms must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the data report forms, which will be documented as being the source data. Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Novartis will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

- IRB/IEC approvals for the study protocol and all amendments
- all source documents and laboratory records
- CRF copies (paper copies or electronic copies on a CD-ROM, depending on the study)
- patients informed consent forms (with study number and title of study)
- any other pertinent study document.

9.6.3 Database management and quality control

Sponsor personnel or a designated representative will review the data entered by investigational staff for completeness and accuracy. When the data collection process is complete for a patient or at specified time points and the data have been validated, the data will be moved to the analysis data set.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the completion of entering data for a patient, the investigator must “electronically certify” or validate that the data for this patient are complete and accurate. At this point, the system will require the investigator to re-enter his password. When the database has been declared to be complete and accurate, the database will be locked.

9.7 Data analysis

All analysis will be performed by Novartis or a designated CRO.

9.7.1 Analysis sets

Full analysis set (FAS): consists of all patients who enroll into the non-interventional study.

Safety set: consists of all patients who had at least one post-baseline safety assessment and were exposed to at least one dose of ruxolitinib. Note that the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment.

9.7.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics including medical history and prior treatment will be summarized descriptively. Categorical data will be summarized by frequency and percentages. Quantitative data will be summarized by the number of patients (n), mean, standard deviation, median, minimum, maximum.

Data will be summarized descriptively and separately for patients exposed and non-exposed to ruxolitinib.

9.7.3 Treatments

Information about ruxolitinib treatment including daily dose, interruptions, and duration of exposure will be summarized by descriptive statistics and corresponding listing will be presented. Treatment with ruxolitinib will be at the discretion of the investigator in accordance with the prescribing information.

Other medications administered for myelofibrosis will be captured and summarized.

9.7.4 Primary objective

The primary objective of this non-interventional study is to document long-term safety in patients with myelofibrosis prescribed ruxolitinib according to the prescribing information.

Data will be summarized descriptively and separately for patients exposed and non-exposed to ruxolitinib.

The incidence of on-treatment Adverse Drug Reactions and SAEs will be summarized by system organ class and preferred term using the MedDRA dictionary. Similar summaries will also be produced for treatment-related SAEs. These listings will cover both events that occur during the on-treatment and post-treatment period however, events that occur during the post- treatment period will be flagged. All ADR and SAE data will be analyzed according to the specifications of the ruxolitinib risk management plan.

9.7.5 Secondary objectives

To document the management of patients with MF.

To document the incidence and outcome of events of special interest.

9.7.6 Interim analyses

No formal interim analyses will be performed. However, descriptive summaries will be prepared annually, for the purposes of reporting Health Authorities.

9.7.7 Sample size and power considerations

A total of approximately 300 MF patients exposed to ruxolitinib are planned for this study. It is expected that about 150 patients not exposed to ruxolitinib will be recruited.

With 300 ruxolitinib exposed patients, there is 95% probability that at least 1 patient will experience an adverse event that has a true probability of occurrence of 1%.

Furthermore, 300 patients exposed to ruxolitinib will provide enough precision to ensure the margin of error on a 95% confidence interval for estimating the rate of specific AEs of interest (herpes zoster, UTI, tuberculosis, bleeding, and intracranial hemorrhage) is less than 5%, assuming the observed rate is similar to what was observed in the COMFORT studies, which was as follows: herpes zoster: 6.5%, UTI: 10.4%, tuberculosis: 0.5%, bleeding (grade 3/4): 4.8%, and intracranial hemorrhage: 4.6%. In addition, 300 patients will provide sufficient probability (>98%) to ensure that the specific AEs of interest of will be observed to occur at least as frequently as what was seen in the pivotal trials assuming the various true occurrence rates as displayed in Table 9-1.

Table 9-1 Probability to observe rates similar to COMFORT studies for specific AEs of interest

AE	Observed rate in Comfort studies	Assumed true rate*	Probability of observing rate at least as high as in Comfort studies
Herpes zoster	0.065	0.13	>0.99
UTI	0.104	0.20	>0.99
Tuberculosis	0.005	0.02	0.98
Bleeding (grade 3/4)	0.048	0.10	>0.99
Intracranial hemorrhage	0.046	0.10	>0.99

* Approximately double observed rate, except for Tuberculosis, which is approximately 4 times observed rate

9.8 Quality control

Data quality assurance

Novartis data management or designated CRO will assure database quality by reviewing the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan

Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient's file. The physician must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

The designated CRO will assure compliance monitoring.

9.9 Limitations of the research methods

Not applicable.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

11 Management and reporting of adverse events/adverse reactions

11.1 Events of special interest

For all patients enrolled in the non-interventional study data for events of special interest will be collected. Events of special interest will be prompted at each visit. For all events of special interest the following information will be collected, where applicable:

1. The severity grade (CTCAE Grade 1-4), event outcome
2. Start and end dates of the event, unless unresolved at final examination, or no further change of the condition can be expected
3. Diagnostic measures and results related to the event, e.g., histopathology, microbiological laboratory results
4. Use of anti-infective therapies, transfusions or other medications related to the management of the event

For patients exposed to ruxolitinib until 28 days after treatment discontinuation, all events of special interest that fulfill the criteria of a SAE will be reported.

Events of special interest are:

Bleeding events

Bleeding events include all hemorrhages of any severity grade (CTCAE 1-4, events with fatal outcome):

- Minor hemorrhages, such as bruising or epistaxis
- Major bleeding events, such as intracranial or intra-abdominal hemorrhages
- Unusual bleedings reported by patients (prolonged or more severe menorrhagia, prolonged bleeding after trauma)

Serious or opportunistic infections

Serious or opportunistic infections are defined as bacterial, viral, fungal or parasitic infections that fulfill one of the following criteria:

- Requires anti-infective treatment
- Leads to significant disability or hospitalization

Secondary malignancies

- Any malignancy diagnosed after inclusion of patients in the non-interventional study will be reported including diagnosis of or progression of MF to AML.

Deaths

- All deaths including cause of death will be reported. Deaths occurring in ruxolitinib exposed patients represent a SAE

11.2 Collection and reporting of Serious Adverse Events and Adverse drug Reactions for ruxolitinib exposed patients

Adverse Drug Reactions to ruxolitinib

For the purpose of this study, an Adverse Drug Reaction (ADR) is defined as a response to ruxolitinib treatment (medical condition, clinical sign, and symptom or laboratory value) which is noxious and unintended. Response in this context means that:

- A causal relationship between ruxolitinib treatment and the event is at least possible as determined by the reporter
- The event occurred after first exposure to ruxolitinib (treatment emergent)

The definition includes worsening of a pre-existing symptom or medical condition.

As data from patients exposed to ruxolitinib as well as unexposed patients will be collected in the non-interventional study and transitions from one cohort to the other are expected, the time window for the collection of ADRs is defined as the first day of exposure to ruxolitinib until 28 days after discontinuation of ruxolitinib.

As much as possible, each ADR should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4), the event outcome
- Confirmation of a reasonable possibility that adverse event is related to ruxolitinib treatment: (no, yes)
- Start and end dates, unless unresolved at final examination, or no further change of the condition can be expected
- Action taken with respect to ruxolitinib (none, dose adjusted, temporarily interrupted, permanently discontinued)
- Whether it is serious, as per SAE definition

Once an adverse reaction is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit of any changes in severity, the suspected relationship to study drug, the interventions required to treat it, and the outcome.

Disease progression should not be regarded or reported as an adverse reaction itself unless associated with a separate adverse reaction, or unless suspected to be related to treatment.

All ADR's will be collected in a dedicated section of the e-CRF and reported in final study report. Interim summaries will be provided to Health Authorities with PSURs.

The occurrence of ADRs and EoSIs should be sought by non-directive questioning of the patient at each visit during the study. ADRs and EoSIs also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All ADRs and EoSIs must be recorded on the safety data collection case report/case record form (CRF) with the information detailed above.

Serious adverse event reporting

An Adverse Event for the purposes of this protocol is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed Informed Consent has been obtained.

An adverse event is categorized as serious (Serious Adverse Event, SAE) if any of the below conditions is fulfilled:

- fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly or a birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for :
  - Routine treatment or monitoring of MF, not associated with any deterioration in condition
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
- is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.
- may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- transmission of infectious agent via medicinal product

Any SAE occurring after the patient has provided informed consent and until 28 days after the patient has permanently discontinued ruxolitinib must be reported to Novartis within 24 hours of learning of its occurrence. Serious adverse events occurring more than 28 days after ruxolitinib discontinuation need to be reported only if a relationship to ruxolitinib is suspected.

In addition, if an RMP exists for the drug of interest any events of special interest must be sent to Novartis DS&E within the same timelines as a serious adverse event in order to facilitate required follow-up.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The treating physician or other involved health care professional must assess the relationship to the drug of interest, complete the SAE Report Form and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) Department. The telephone and telefax number of the contact persons in the local department of DS&E, specific to the site, are listed in the treating physician or other involved health care health care professional folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Of note, SAEs that are suspected to be causally related to ruxolitinib treatment must also be recorded as an ADR.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Package Insert a local DS&E Department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

Pregnancies

Any pregnancy occurring in a patient participating in the non-interventional study (ruxolitinib exposed and unexposed patients) will be recorded and should be followed to determine outcome, including spontaneous or induced termination, details of the birth, the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancies reported in a patient receiving ruxolitinib treatment must be reported to Novartis within 24 hours of learning of its occurrence. These should be recorded on a Pregnancy Form for reporting to the local Novartis Drug Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities or birth defects, maternal or newborn complications and their relation to Ruxolitinib. Follow-up on pregnancies will be done on a quarterly basis. Any SAE experienced during pregnancy must be reported as an SAE.

12 Plans of disseminating and communicating study results

Prior to initiation, the non-interventional study will be published at publically administered study data base including information on study type and design.

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

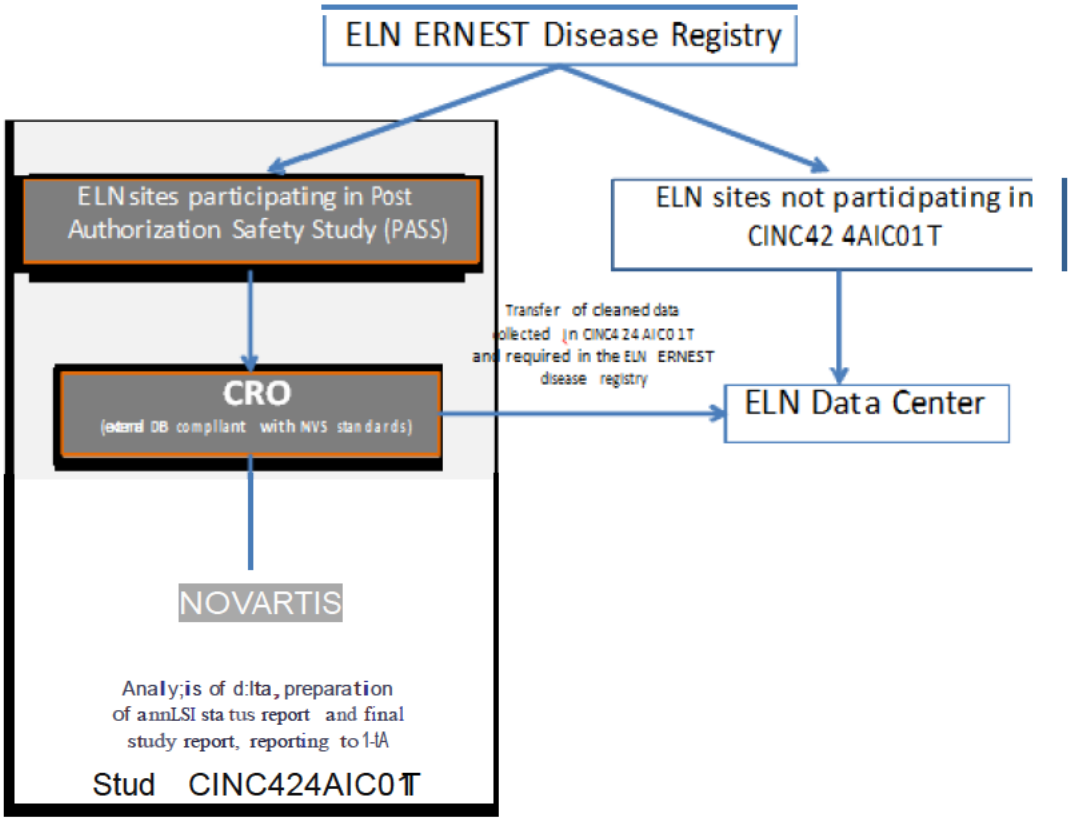
For non-interventional PASS studies, the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

Data flow and cooperation with the ELN registry

This MF disease registry is planned to be conducted at 100 sites collaborating with the European Leukemia Net (ELN), an academic network of excellence dedicated to improve the treatment of patients with hematologic malignancies. The ELN is preparing a European Registry for Myeloproliferative Disorders (ERNEST). The ERNEST registry will collect data on disease risk factors and outcome data of representative samples of patients with myeloproliferative neoplasms of major European countries. It is planned that selected ERNEST sites who have received specific training and who have adequate resources for the long-term follow-up of patients will be contributing patients to both the ERNEST registry as well as the MF non-interventional study.

It is acknowledged, that the data emerging from this MF non-interventional study will be of relevance for the ELN ERNEST registry. Therefore the data will be collected in a format that allows transmission from the MF non-interventional study data base to the ELN data base and enabling ELN to use data from the MF non-interventional study together with the data from their ERNEST registry. To assure safety reporting consistent with Volume 9a of the Rules of Medicinal Products in the EU and analysis of the data in its entirety, safety data (ADRs, SAEs and Pregnancies) related to ruxolitinib exposed patients will be managed by Novartis and not transferred to the ERNEST registry. The data flow is shown in Figure 12-1.

Figure 12-1 Data flow non-interventional study and ERNEST Registry



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14 Annexes

14.1 Annex 1 List of stand-alone documents

None.

14.2 Annex 2 ENCePP checklist for study protocol

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Non-Interventional Long-term Safety Study of Ruxolitinib in Myelofibrosis

Study reference number:
CINC424AIC01T ENCePP number 3296

Section 1: Milestones	**Yes**	**No**	**N/A**	**Protocol section(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	4
1.1.5 Registration in the EU PAS register	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

1.1.4 yearly PSUR

Section 2: Research question	**Yes**	**No**	**N/A**	**Protocol section(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

No

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Protocol section(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	4/8
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	

Comments:

No

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Protocol section(s)**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:	☒	☐	☐	4
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☒	☐	☐	Cover page
4.2.3 Country of origin?	☒	☐	☐	9.1/9.2.1
4.2.4 Disease/indication?	☐	☒	☐	
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

4.2.2 age is defined as adult patients; sex in not defined

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Protocol section(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☒	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Protocol section(s)**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

No

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Protocol section(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	9.7
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

No

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Protocol section(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	

Comments:

No

Section 8: Data sources	**Yes**	**No**	**N/A**	**Protocol section(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.7.3
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.6.2/9.3
8.1.3 Covariates?	☐	☒	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Protocol section(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☒	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	4/9.2.2
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	9.3.4/9.6.3/9.7.4
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.6.3
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

No

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Protocol section(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	9.7.7

Comments:

No

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Protocol section(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

No

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Protocol section(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.2/9.63
11.3 Are methods of quality assurance described?	☒	☐	☐	9.8
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

No

Section 12: Limitations	**Yes**	**No**	**N/A**	**Protocol section(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☒ ☒	☐ ☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.1.2
12.3 Does the protocol address other limitations?	☒	☐	☐	9.1.2

Comments:

No

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Protocol section(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	5
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

No

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Protocol section(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	5

Comments:

No

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Protocol section(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

No