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Protocol Page

Administration of Jakafi (Ruxolitinib) to Patients with Previously Untreated High-Risk Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): A Phase II Clinical Trial

2015-0570

Core Protocol Information

Short Title	Administration of Jakafi (Ruxolitinib) to Patients with Previously Untreated High-Risk CLL: A Phase II Clinical Trial
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Full Title:	Administration of Jakafi (Ruxolitinib) to Patients with Previously Untreated High-Risk Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL): A Phase II Clinical Trial
Public Description:	BACKGROUND: Disease-related symptoms impair the quality of life of patients with chronic lymphocytic leukaemia (CLL) who do not require systemic therapy. Available therapies are not specifically aimed at symptom control. Because stimulation of the B-cell receptor activates JAK2 in CLL cells and the JAK2 inhibitor ruxolitinib improves symptoms in patients with myelofibrosis, we postulated that ruxolitinib would improve disease-related symptoms in patients with CLL. We did a phase 2 trial of ruxolitinib to test this hypothesis. METHODS: Symptomatic patients with CLL who did not require systemic therapy were enrolled at MD Anderson Cancer Center (Houston, TX, USA) between Sept 15, 2014, and Sept 20, 2015. Participants were given 10 mg ruxolitinib orally twice a day. Scores on the Brief Fatigue Inventory (BFI), CLL module of the MD Anderson Symptom Inventory (MDASI) and symptom-associated interference in daily activities, were assessed before treatment and after 3 months. This trial is ongoing and is registered at ClinicalTrials.gov (NCT02131584). FINDINGS: 41 patients (25 previously untreated for CLL and 16 previously treated) were enrolled. At 3 months, the mean percentage change from baseline in BFI score was 44·3% (SD 35·0, p<0·0001), in symptom interference score was 43·4% (51·5, p<0·0001), and in MDASI score was 42·1% (37·4, p<0·0001). 32 (78%) of the patients experienced 20% or greater reduction in the mean BFI, and 24 (59%) had a reduction of two units or more in worst fatigue score in past 24 hours as assessed by the BFI. The most comment grade 3-4 adverse events were neutropenia (n=2 [5%]), hypertension (n=2 [5%]), insomnia (n=1 [2%]), tinnitus and dizziness (n=1 [2%]), and thrombocytopenia (n=1 [2%]). INTERPRETATION: In patients with CLL, ruxolitinib was associated with significant improvements in disease-related symptoms as measured by BFI, MDASI, and symptom interference scores. As of now, 60 patients have been enrolled. Analysis of these patients' outcome is pending.
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Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

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ADMINISTRATION OF JAKAFI (RUXOLITINIB) TO PATIENTS WITH PREVIOUSLY UNTREATED HIGH-RISK CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)/SMALL LYMPHOCYTIC LYMPHOMA (SLL): A PHASE II CLINICAL TRIAL

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1.0 OBJECTIVES

1.1 Primary Objectives

To determine the effect of ruxolitinib in patients with high-risk CLL/SLL who do not require anti-neoplastic therapy according to the IWCLL 2008 recommendations and were either previously untreated or treated with Ibrutinib for less than 3 months and were deemed Ibrutinib intolerant: a.) On disease burden, and b.) The rate of complete response (CR) and partial response (PR) as assessed by the IWCLL 2008 response criteria.

1.2 Secondary Objective

To evaluate the time to next treatment in high-risk CLL/SLL who do not require anti-neoplastic therapy according to the IWCLL 2008 recommendations.

2.0 BACKGROUND

2.1 Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lyphoma (SLL)

B-cell chronic lymphocytic leukemia (CLL), the most common leukemia in the Western hemisphere, is characterized by a dynamic imbalance between the proliferation and apoptosis of neoplastic B-lymphocytes co-expressing CD19, CD5 and CD23 antigens. The clinical course of the disease is variable. At the time of diagnosis, most patients have an indolent disease that might require therapy several years thereafter or no treatment at all. The life expectancy of the latter group is similar to that of age-matched healthy individuals. However, a significant number of patients present with a rapidly progressive disease that requires immediate therapeutic intervention.

Recently, oral agents that inhibit the B cell receptor (BCR) of CLLSLL cells became available. The currently available BCR inhibitors have a variety of side effects that will make a significant number of elderly patients with CLL/SLL ineligible for treatment with these agents. In a phase III clinical trial of the Bruton tyrosine kinase (BTK) inhibitor Ibrutinib Vs. chlorambucil (Burger JA., et al. N Engl J Med 2015; 373:2425-37), that ultimately led to the approval of Ibrutinib for untreated patients with CLL/SLL, the side effects of Ibrutinib included diarrhea in 42% of the patients (including grade 3 diarrhea in 4%), and fatigue, nausea, and cough in 20% or more of the patients. In addition, hypertension was observed in14% of the patients with grade 3 hypertension occurring in 4%,atrial fibrillation occurred in 6%, major hemorrhage (defined as any serious or grade 3 or higher hemorrhage or central nervous system hemorrhage of any grade) occurred in 4% of the patients. Furthermore, Ibrutinib-resistant clones were found in a significant number of Ibrutinib-treated patients and the clinical outcome of these patients is dire (Furman RR et al. N Engl J Med. 2014; 370:2352-4; Woyach JA et al. N Engl J Med. 2014; 370:2286-94; Burger JA et al. Nat Commun. 2016; May 20; 7:11589).

Another BCR ibhibitor Idelalisib, an oral inhibitor of PI3Kδ that has substantial activity in patients with relapsed/refractory CLL induces transaminase elevation that led to discontinuation of the drug in 45.3%, diarrhea in 12.5%, and colitis in 6.3% of the patients. In addition, Idelalisib induced in dyspnea in 4.7%, pneumonia in 17.2%, and rash in 4.7% of the patients (O'Brien SM et al., Blood 2016; 126:2686-2694). Remarkably, The European Medicines Agency (EMA) Committee for Medicinal Products for Human studies apprehended the Idelalisib study in Europe because of deaths in 3 patients. Eventually, the study re-opened with specific strict precautions (www.gilead.com).

Although other BTK and PI3K inhibitors are currently investigated in clinical trials, the activity of Ruxolitinib, an agent that targets a different pathway and has a different side effect profile is warranted as it addresses an unmet need.

Although approximately 20% of CLL patients are diagnosed as a result of routine blood tests, most patients present with a wide range of symptoms typically witnessed in chronic inflammatory diseases (Hallek et al., 2008).

The role of cytokines and chemokines in the pathogenesis, maintenance, and progression of CLL has been the subject of intense research over the past two decades. In culture, CLL cells undergo spontaneous apoptosis (Collins et al., 1989). However, co-culture with T lymphocytes, mesenchymal stromal cells (MSC), nurse-like cells (NLCs), or endothelial cells, significantly reduces apoptosis rates of CLL cells (Badoux et al. 2011; Burger JA, 2011), suggesting that soluble factors and cell-to-cell interactions provide CLL cells with survival signals. Various cytokines whose levels are not increased in CLL also play a role in this process. For example, IL-4 activates the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway that protects CLL cells from chemotherapy-induced apoptosis (Dietrich et al., 2012). Although IL-4 levels are not elevated in the serum of patients with CLL (Yan et al. 2011), IL-4 receptor levels are constitutively high in CLL cells (Douglas et all., 1997). Similarly, BAFF, a member of the TNF superfamily, is thought to provide CLL cells with a survival advantage (Kern et al., 2004). As found in our laboratory, activation of the B-cell receptor activates JAK2 in CLL cells and, like in other inflammatory conditions (Ivanenkov et al., 2008; Vijayakrishnan et al., 2011) inhibition of JAK2 induces apoptosis of CLL cells.

Two large-scale DNA deep-sequencing studies detected somatic mutations in CLL cells. In one study, deep sequencing of 105 CLL samples detected 1246 mutations affecting 1100 protein-coding genes (Quesada et al., 2012). In another study, parallel exome and whole genome sequencing of 91 CLL samples detected 1838 non-synonymous mutations in 1608 protein coding genes (Wang et al., 2012). Surprisingly, only 186 recurrent and non-recurrent mutations were identified simultaneously in both data sets. In spite of the limited overlap in mutation detection, the mutated genes were clustered in similar pathways in the two data sets with an overwhelming representation of pro-inflammatory pathways.

In a comprehensive analysis of 23 cytokines in the sera of 84 patients with CLL and 49 age-matched healthy individuals, the levels of 17 cytokines, mostly inflammatory cytokines, were significantly higher in the serum of patients with CLL (Yan et al. 2011). More than 14-fold increase in INF-γ was found in the serum of untreated CLL patients (Mahadevan et al., 2009). Similarly, plasma levels of IL-1, IL-6, IL-10 (Fayad et al., 2001), IL-8, and TNF-α (Yoon et al., 2012) were also typically increased. The majority of those inflammatory cytokines are produced as a result of activation of the transcription factor κB, known to be constitutively activated in CLL cells (Liu et al., 2010) and several of them (such as IL-6) bind to their corresponding receptors and activate JAK1. Most of those cytokines are known to be responsible for signs and symptoms of inflammatory diseases. Whether produced by CLL or other cells, these cytokines contribute both directly and indirectly, to the survival of CLL cells and to the signs and debilitating symptoms of patients with CLL.

In various neoplastic cells activation of the JAK/STAT pathway provides cells with survival advantage. In a recent study (Rozovski et al., 2014) we investigated whether activation of the B-cell receptor (BCR) activates the JAK/STAT pathway. To stimulate the BCR we incubated CLL cells with anti-IgM antibodies. We found that activation of the BCR induces activation of JAK2, which phosphorylates STAT3. Incubation of CLL cells with the JAK1/2 inhibitor ruxolitinib inhibited IgM-induced STAT3 phosphorylation and induced apoptosis of IgM-stimulated but not unstimulated CLL cells in a dose- and time-dependent manner. Therefore we sought to determine whether treatment with ruxolitinib would benefit patients with CLL. If ruxolitinib is found be effective we intend to further develop it for the treatment of CLL.

2.1.1 Effect of Ruxolitinib in patients with CLL/SLL

Because no standard therapeutic intervention is available to control CLL/SLL patients' symptoms and because stimulation of the BCR activates the JAK/STAT3 pathway, known to induce the production of inflammatory cytokines (Rozovski et al., 2014), we conducted a clinical trial (protocol 2013-0044) to assess the effect of ruxolitinib on symptoms in CLL/SLLpatients. After the enrollment of 40 patients onto this study we found that: **1.)** Ruxolitinib is well tolerated in patients with CLL/SLL. Very few patients had to be removed from the study because of adverse events. **2.)** The vast majority of the patients (78 %) responded to therapy, their symptoms improved, often dramatically, and the clinical improvement in the patients correlated with a significant reduction in plasma inflammatory cytokine levels. **3.)** In several patients, the number of peripheral blood lymphocyte counts increased and then decreased to or below baseline level, as observed in CLL/SLL patients treated with the Bruton tyrosine kinase (BTK) inhibitor Ibrutinib, suggesting that, like Ibrutinib, ruxolitinib induces mobilization and then apoptosis of CLL/SLL cells. Therefore we intend to explore whether ruxolitinib would reduce disease burden in patients with high-risk CLL/SLL.

2.1.2 Previously untreated patients with high-risk CLL/SLL

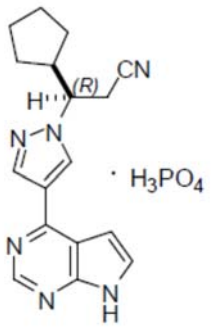
The clinical course of patients with CLL/SLL is diverse; some patients have indolent disease, never needing treatment, whereas others have aggressive disease requiring early intervention. We currently use clinical criteria to initiate therapy. Hoewever several investigators suggested that early intervention in patients with high-risk disease might be beneficial. To determine which patients are at high risk of disease progression, a multivariable analysis was performed to identify prognostic factors independently associated with time to first treatment for patients with CLL (Wierda et al., 2011). This multivariable model was used to develop a nomogram-a weighted tool to calculate 2- and 4-year probability of treatment and estimate median time to first treatment.

The factors independently associated with shorter time to first treatment included: **a.)** three involved lymph node sites, **b.)** increased size of cervical lymph nodes, **c.)** presence of 17p deletion or 11q deletion assessed by fluorescence in situ hybridization (FISH), increased serum lactate dehydrogenase (LDH), and unmutated IgHV (Wierda et al., 2011).

Given that ruxolitinib is well tolerated and efficiently alleviates the symptoms of patients with CLL/SLL and given that, similar to Ibrutinib, treatment with ruxolitinib increased and then reduced the number of circulating lymphocytes, we sought to investigate the clinical benefits of ruxolitinib in patients with previously untreated high-risk CLL/SLL. In particular, we intend to study the effect of ruxolitinib on disease burden and determine whether treatment with ruxolitinib will delay the time to next treatment of previously untreated patients with high-risk CLL/SLL who are expected to require therapy for CLL/SLL within 4 years according to the above described nomogram (Wierda et al., 2011).

2.2 Ruxolitinib (Jakafi)

Ruxolitinib phosphate is a kinase inhibitor with the chemical name (*R*)-3-(4-(7*H*-pyrrolo[2,3- *d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36. Ruxolitinib phosphate has the following structural formula:



Ruxolitinib phosphate is a white to off-white to light pink powder and is soluble in aqueous buffers across a pH range of 1 to 8. Jakafi (ruxolitinib) Tablets are for oral administration. Each tablet contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

2.2.1 Mechanism of Action

Ruxolitinib is a kinase inhibitor that inhibits the Janus kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Myelofibrosis (MF) and polycythemia vera (PV) are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (e.g., TNF-α, IL-6).

2.2.2 Pharmacodynamics

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and patients with MF and PV. Ruxolitinib administration resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 10 hours in both healthy subjects and patients with MF and PV.

2.2.3 Pharmacokinetics

Absorption. In clinical studies, ruxolitinib is rapidly absorbed after oral ruxolitinib (Jakafi) administration with maximal plasma concentration (C_{max}) achieved within 1 to 2 hours post-dose. Based on a mass balance study in humans, oral absorption of ruxolitinib was estimated to be at least 95%. Mean ruxolitinib C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There were no clinically relevant changes in the pharmacokinetics of ruxolitinib upon administration of Jakafi with a high-fat meal, with the mean C_{max} moderately decreased (24%) and the mean AUC nearly unchanged (4% increase).

Distribution. The mean volume of distribution at steady-state is 72 L in patients with MF with an associated inter-subject variability of 29% and 75 L in patients with PV with an associated inter-subject variability of 23%. Binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin.

Metabolism. In vitro studies suggest that ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

Elimination. Following a single oral dose of [14C]-labeled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity. The mean elimination half-life of ruxolitinib is approximately 3 hours and the mean half-life of ruxolitinib + metabolites is approximately 5.8 hours.

Effects of Age, Gender, or Race. In healthy subjects, no significant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in patients with MF, no relationship was apparent between oral clearance and patient age or race, and in women, clearance was 17.7 L/h and in men, 22.1 L/h with 39% inter-subject variability. Clearance was 12.7 L/h in patients with PV, with a 42% inter-subject variability, and no relationship was apparent between oral clearance and gender, patient age or race in this patient population.

2.2.4 Drug Interactions

Strong CYP3A4 inhibitors: In a trial of 16 healthy volunteers, a single dose of 10 mg of Jakafi was administered alone on Day 1 and a single dose of 10 mg of Jakafi was administered on Day 5 in combination with 200 mg of ketoconazole (a strong CYP3A4 inhibitor, given twice daily on Days 2 to 5). Ketoconazole increased ruxolitinib C_{max} and AUC by 33% and 91%, respectively. Ketoconazole also prolonged ruxolitinib half-life from 3.7 to 6.0 hours.

Fluconazole: Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady state ruxolitinib AUC by approximately 100% to 300% following concomitant administration of 10 mg of Jakafi twice daily with 100 mg to 400 mg of fluconazole once daily, respectively.

Mild or moderate CYP3A4 inhibitors: In a trial of 15 healthy volunteers, a single dose of 10 mg of Jakafi was administered alone on Day 1 and a single dose of 10 mg of Jakafi was administered on Day 5 in combination with 500 mg of erythromycin (a moderate CYP3A4 Inhibitor, given twice daily on Days 2 to 5). Erythromycin increased ruxolitinib C_{max} and AUC by 8% and 27%, respectively.

CYP3A4 inducers: In a trial of 12 healthy volunteers, a single dose of 50 mg of Jakafi was administered alone on Day 1 and a single dose of 50 mg of Jakafi was administered on Day 13 in combination with 600 mg of rifampin (a strong CYP3A4 inducer, given once daily on Days 3 to 13). Rifampin decreased ruxolitinib C_{max} and AUC by 32% and 61%, respectively. In addition, the relative exposure to ruxolitinib active metabolites increased approximately 100%.

In vitro studies: *In vitro*, ruxolitinib and its M18 metabolite do not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Ruxolitinib is not an inducer of CYP1A2, CYP2B6 or CYP3A4 at clinically relevant concentrations. *In vitro*, ruxolitinib and its M18 metabolite do not inhibit the P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport systems at clinically relevant concentrations. Ruxolitinib is not a substrate for the P-gp transporter.

Thorough QT interval Study: The effect of single dose ruxolitinib 25 mg and 200 mg on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 47 healthy subjects. The study demonstrated the ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 200 mg is adequate to represent the high exposure in a clinical scenario.

2.2.5 Nonclinical toxicity

Carcinogenesis, Mutagenesis, Impairment of Fertility: Ruxolitinib was not carcinogenic in the 6-month Tg.rasH2 transgenic mouse model or in a 2-year carcinogenicity study in the rat. Ruxolitinib was not mutagenic in a bacterial mutagenicity assay (Ames test) or clastogenic in *in vitro* chromosomal aberration assay (cultured human peripheral blood lymphocytes) or *in vivo* in a rat bone marrow micronucleus assay. In a fertility study, ruxolitinib was administered to male rats prior to and throughout mating and to female rats prior to mating and up to the implantation day (gestation day 7). Ruxolitinib had no effect on fertility or reproductive function in male or female rats at doses of 10, 30 or 60 mg/kg/day. However, in female rats doses of greater than or equal to 30 mg/kg/day resulted in increased post-implantation loss.The exposure (AUC) at the dose of 30 mg/kg/day is approximately 34% the clinical exposure at the maximum recommended dose of 25 mg twice daily.

2.2.6 Drug product

Formulation: Ruxolitinib (Jakafi®) is commercially available in the US in 5, 10, 15, 20, and 25 mg strength tablets. The tablet contains the active ingredient and may include the following commonly used excipients: microcrystalline cellulose, lactose, stearic acid, magnesium stearate, colloidal silicone dioxide, sodium starch glycolate, Povidone, and hydroxyl propyl cellulose. All excipients are of US and EuPh compendial grade.

The 5 mg (free base equivalent) and 25 mg (free base equivalent) tablets are packaged in HDPE bottles. All bottles of Incyte investigational product contain the following language: “Caution: New Drug-Limited by Federal Law to Investigational Use.” The clinical supply for investigational use is the 5 mg tablet.

Storage and stability: Ruxolitinib has been shown to be stable for up to 6 months at 40°C and up to 24 months when stored at 25°C.

Compatibility: Ruxolitinib may be taken either with food or without food

Handling: Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Availability: Ruxolitinib will be supplied free-of-charge from Incyte in 5 mg tablets.

2.2.7 Human pharmacokinetics

Ruxolitinib exhibits near complete oral absorption, achieving maximal plasma concentration at approximately 1-2 h post-dose with linear PK over a dose range of 5-200 mg. Ruxolitinib is mainly eliminated by metabolism via CYP3A4 with minor contributions of CYP2C9 with a terminal elimination half-life of approximately 3 h. Administration with food did not affect ruxolitinib overall exposure. Ruxolitinib may be administered without regard to meals.

When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose of ruxolitinib should be decreased by approximately 50% based on the platelet counts (or as specified in country-specific product labels). No dose adjustment is necessary when a mild or moderate CYP3A4 inhibitor is used as concomitant medication (although patients should be monitored closely for cytopenias when starting a mild or moderate CYP3A4 inhibitor). Upon initiation of a CYP3A4 inducer, no dose adjustment is recommended. Gradual dose increases of ruxolitinib may be considered if the effectiveness of therapy is diminished during chronic treatment with a CYP3A4 inducer.

In patients with moderate (CrCl 30-50 mL/min) and severe renal impairment (CrCl <30 mL/min), the recommended starting dose should be based on platelet count and reduced by approximately 50% (or as specified in country specific product labels). Available data in patients with end stage renal disease suggests that patients on hemodialysis should initiate dosing with a single dose of 15 mg or 20 mg following each hemodialysis, based on platelet counts, with subsequent doses following each hemodialysis session and administered only on dialysis days with careful monitoring of safety and efficacy. Doses in patients with renal impairment should be subsequently adjusted based on individual safety and efficacy.

Although ruxolitinib exposure was increased in subjects with hepatic impairment, there was no relationship between ruxolitinib exposure and the degree of hepatic impairment as determined by the Child-Pugh score. Conservatively, in patients with any degree of hepatic impairment, the recommended starting ruxolitinib dose should be based on platelet count and reduced by approximately 50% (or as specified in country specific product labels). Patients developing any hepatic impairment during treatment should be carefully monitored and may have their doses reduced to avoid toxicity. Further dose modifications should be based on the safety and efficacy.

2.2.8 Safety and efficacy

The safety profile for ruxolitinib in the Phase I development program was assessed in over 145 healthy subjects for single doses from 5 mg to 200 mg, and in 53 healthy subjects for repeat doses from 15 mg to 50 mg b.i.d. and 50 to 100 mg q.d. Ruxolitinib has also been administered to 32 subjects with various degrees of renal impairment, 24 subjects with various degrees of hepatic impairment, and 50 subjects with rheumatoid arthritis (RA). Adverse events (AEs) were, in general, mild and resolved without interventions. In the first in human study one subject had hyponatremia after receiving 5

mg ruxolitinib. The hyponatremia was assessed as severe in intensity, unrelated to study medication, reversed within 5 days, and was reported as a serious adverse event (SAE).

In the repeat-dose study in healthy subjects, the intensity of an AE was graded according to the protocol-defined toxicity criteria based on Rheumatology Common Toxicity Criteria V 1.0. The dose-limiting AE was neutropenia, which occurred at a dose of 50 mg b.i.d. Neutropenia as an AE was noted in three subjects, all receiving the highest dose of ruxolitinib, 50 mg b.i.d. Neutropenia at the Grade 4 level, assessed as severe, led to study drug discontinuation on Day 5 in one subject, and was reported as a SAE. Neutrophil count returned to a normal level 12 days after the final dose of study medication. In two other subjects, neutropenia was Grade 1 or 2, and resolved with dose interruption or during continued dosing. The AE profile was similar for single- and multiple-dose studies, and no differences were observed between males and females. The most frequent (≥2subjects) treatment-emergent AEs (TEAEs) occurring in the Phase I multiple-dose study were: neutropenia (4.2%), dizziness (2.8%), headache (2.8%) and nausea (2.8%). Overall, in healthy volunteer studies where frequent sampling of the neutrophil count was performed, a transient, reversible decrease in neutrophil count was frequently seen following dosing, which reversed after 12-24 h off drug.

2.2.8.1 Studies in myelofibrosis (MF)

Three studies enrolled patients with MF for which data has been reported as per planned analyses. Phase I/II study enrolled 158 patients in the target disease population of PMF, PPV-MF, and PET-MF to establish safety, efficacy, MTD, dose limiting toxicities, and appropriate dose regimens for the Phase III studies. The Phase III clinical program consists of two studies: study, conducted in the USA, Canada and Australia, which is a placebo controlled study that enrolled 309 patients and study conducted in Europe, which compares ruxolitinib with BAT in 219 patients. Those phase III trials (COMFORT I and II) confirmed the findings observed in the phase I/II studies.

In general, in the phase I/II studies the proportions of patients showing improvement were similar across dose cohorts. At Week 24, nine patients (42.9%) who started at 10 mg b.i.d., 16 patients (51.6%) who started at 15 mg b.i.d., 15 patients (37.5%) who started at 25 mg b.i.d., three patients (75.0%) who started at 50 mg b.i.d., and 11 (37.9%) patients who started with a q.d. dose regimen showed clinical improvement. Among the b.i.d. treatment arms, patients who initiated dosing at 15 mg b.i.d. and had subsequent optimization of treatment showed the highest consistent response rate over time through Cycle 16 (Week 60).

Reduction in spleen size: At the first assessment (Week 4), 37.7% of patients had a ≥50% reduction from baseline in spleen length assessed by palpation. At Week 24 (6 months of treatment), 43.8% of patients had a ≥50% reduction from baseline in spleen length. The median percent reduction from baseline in spleen length assessed by palpation was approximately 52% at Week 24 and 63% at Week 60 (Verstovsek et al., 2010, Verstovsek et al., 2012).

Improvement in symptom scores: In this study a modified MFSAF questionnaire was used (questionnaire consisting of 15 common signs and symptoms experienced by patients in MF), which was a predecessor of the one utilized in the Phase III MF studies. This improvement was generally maintained over time; at Week 60, the median percent reduction from baseline was 65%. (Verstovsek et al., 2010; Mesa et al., 2011; Verstovsek et al., 2012).

Increase in body weight: Patients showed a gradual increase in body weight over the course of the study. It is important to note that weight gain in this population may be a positive response, as splenomegaly causes early satiety and constitutional symptoms of anorexia are common. When examined by baseline body mass index (BMI) quartile, the four groups generally gained weight consistently over time. Further, assessment of the percent change from baseline showed that the lowest BMI group gained the most weight and the highest BMI group gained the least weight (Verstovsek et al., 2010; Mesa et al., 2011; Verstovsek et al., 2012).

Improvement in overall survival: A Kaplan-Meier estimate of overall survival (OS) showed that the probability of survival was 96% at 1 year and 90% at 2 years. (Verstovsek et al., 2012).

Improvement in symptoms and QoL: Symptoms of MF were assessed using a symptom diary (modified MFSAF v2.0 diary, electronic device). Improvement in MF symptoms and QoL correlated with a reduction in inflammatory cytokine levels (Verstovsek et al., 2010; Mesa et al., 2011; Verstovsek et al., 2012).

2.2.9 Adverse events

A summary of most frequently (≥5%) reported AEs in the Phase III population regardless of study drug relationship by preferred term is presented in Table 1. The comparison of the control groups to the ruxolitinib patients showed that headache was more frequent in ruxolitinib-treated patients (13.6% vs. 6.0% on placebo and 5.5% on BAT). Most AEs of headache were Grade 1 or 2. Similarly, dizziness (12.0% vs. 6.6% on placebo and 6.8% on BAT) was more frequent in ruxolitinib-treated patients, again mostly Grade 1 or 2. When adjusted for patient-year exposure, the differences are still present for headache and dizziness.

Weight increase was also more frequent in ruxolitinib-treated patients than in the control groups (9.6% vs. 1.3% on placebo and 1.4% on BAT). Although some of these patients had co-reported AEs of edema, many had a past medical history of weight loss and the weight gain usually gradually accumulated over the course of one year of treatment. The majority of weight gain AEs were Grade 1 and 2. It is worth noting that weight gain may be a beneficial effect in patients with MF, given the catabolic nature of the disease and the frequency of weight loss reported as a constitutional symptom.

Other preferred terms with increased frequency in the ruxolitinib arms included bruising

(2.6% vs. 1.3% on placebo in, contusion (8.6% vs. 5.3% on placebo herpes zoster (4.0% vs. 0.7% on placebo and 0% on BAT) and flatulence (3.3% vs. 1.3% on placebo and 0% on BAT). Abdominal pain was more frequent in the control groups than in the ruxolitinib group (43% on placebo and 13.7% on BAT vs. 12% on ruxolitinib), as were weight decrease (8.6% on placebo and 8.2% on BAT vs. 1% on ruxolitinib), early satiety (8.6% on placebo and 0% on BAT vs. 0.3% on ruxolitinib) and splenic infarction (6.0% on placebo and 0% on BAT vs. 1.0% on ruxolitinib).

Table 1. Most frequently reported adverse events (AEs) in a Phase III clinical trial

	Study INCB 18424-351		**Study CINC424A2352**		**Total**
	Ruxolitinib N=155 n (%)	**Placebo N=151 n (%)**	**Ruxolitinib N=146 n (%)**	**BAT N=73 n (%)**	**Ruxolitinib N=301 n (%)**
Any	**152 (98.1)**	**149 (98.7)**	**145 (99.3)**	**67 (91.8)**	**297 (98.7)**
Thrombocytopenia	58 (37.4)	14 (9.3)	65 (44.5)	9 (12.3)	123 (40.9)
Anemia	49 (31.6)	22 (14.6)	61 (41.8)	10 (13.7)	110 (36.5)
Diarrhea	37 (23.9)	35 (23.2)	38 (26.0)	11 (15.1)	75 (24.9)
Edema peripheral	31 (20.0)	36 (23.8)	34 (23.3)	19 (26.0)	65 (21.6)
Fatigue	43 (27.7)	54 (35.8)	19 (13.0)	8 (11.0)	62 (20.6)
Dyspnea	28 (18.1)	28 (18.5)	24 (16.4)	13 (17.8)	52 (17.3)
Nausea	23 (14.8)	29 (19.2)	21 (14.4)	5 (6.8)	44 (14.6)
Headache	24 (15.5)	9 (6.0)	17 (11.6)	4 (5.5)	41 (13.6)
Pyrexia	19 (12.3)	12 (7.9)	22 (15.1)	7 (9.6)	41 (13.6)
Cough	18 (11.6)	13 (8.6)	22 (15.1)	12 (16.4)	40 (13.3)
Pain in extremity	22 (14.2)	16 (10.6)	17 (11.6)	3 (4.1)	39 (13.0)
Arthralgia	18 (11.6)	14 (9.3)	19 (13.0)	7 (9.6)	37 (12.3)
Abdominal pain	19 (12.3)	65 (43.0)	17 (11.6)	10 (13.7)	36 (12.0)
Dizziness	25 (16.1)	10 (6.6)	11 (7.5)	5 (6.8)	36 (12.0)
Vomiting	20 (12.9)	17 (11.3)	16 (11.0)	1 (1.4)	36 (12.0)
Asthenia	8 (5.2)	12 (7.9)	26 (17.8)	7 (9.6)	34 (11.3)
Nasopharyngitis	7 (4.5)	9 (6.0)	27 (18.5)	10 (13.7)	34 (11.3)
Constipation	21 (13.5)	19 (12.6)	11 (7.5)	4 (5.5)	32 (10.6)
Weight increased	13 (8.4)	2 (1.3)	16 (11.0)	1 (1.4)	29 (9.6)
Hemoglobin decreased	23 (14.8)	6 (4.0)	4 (2.7)	3 (4.1)	27 (9.0)
Insomnia	18 (11.6)	15 (9.9)	9 (6.2)	5 (6.8)	27 (9.0)
Back pain	11 (7.1)	13 (8.6)	15 (10.3)	9 (12.3)	26 (8.6)
Contusion	23 (14.8)	8 (5.3)	3 (2.1)	1 (1.4)	26 (8.6)
Platelet count decreased	15 (9.7)	4 (2.6)	11 (7.5)	2 (2.7)	26 (8.6)
Muscle spasms	11 (7.1)	11 (7.3)	14 (9.6)	5 (6.8)	25 (8.3)
Night sweats	12 (7.7)	18 (11.9)	13 (8.9)	6 (8.2)	25 (8.3)
Abdominal pain upper	10 (6.5)	13 (8.6)	12 (8.2)	4 (5.5)	22 (7.3)
Bronchitis	4 (2.6)	2 (1.3)	18 (12.3)	5 (6.8)	22 (7.3)
Urinary tract infection	12 (7.7)	7 (4.6)	10 (6.8)	2 (2.7)	22 (7.3)
Epistaxis	9 (5.8)	8 (5.3)	12 (8.2)	5 (6.8)	21 (7.0)
Abdominal distension	13 (8.4)	17 (11.3)	5 (3.4)	1 (1.4)	18 (6.0)
Cardiac murmur	12 (7.7)	5 (3.3)	6 (4.1)	3 (4.1)	18 (6.0)

Hematoma	4 (2.6)	0	14 (9.6)	3 (4.1)	18 (6.0)
Pneumonia	13 (8.4)	11 (7.3)	4 (2.7)	5 (6.8)	17 (5.6)
Rash	9 (5.8)	8 (5.3)	8 (5.5)	1 (1.4)	17 (5.6)
Dyspnea exceptional	6 (3.9)	5 (3.3)	10 (6.8)	2 (2.7)	16 (5.3)
Paraesthesia	6 (3.9)	4 (2.6)	10 (6.8)	4 (5.5)	16 (5.3)
Dyspepsia	9 (5.8)	8 (5.3)	6 (4.1)	4 (5.5)	15 (5.0)

The most frequently occurring Grade 3 and 4 AEs regardless of study drug relationship were hematologic including anemia (14%) and thrombocytopenia (8%). Non-hematologic Grade 3-4 AEs were infrequent and rarely reported more frequently than in the control arms. Two patients (0.7%) had febrile neutropenia. In general, the pattern of AEs was similar between the two ruxolitinib arms in both studies, although there were some differences in frequency for specific AEs.

In the clinical study program the severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1 = mild, grade 2 = moderate, grade 3 = severe and grade 4=life threatening.

Adverse drug reactions from clinical studies (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2. Percent of patients with adverse drug reactions

ADRs and CTCAE Grade	**INCB 18424-351**		**CINC424A2352**		**Total Ruxolitinib N=301**	**Frequency category**
	Ruxolitinib N=155	**Placebo N=151**	**Ruxolitinib N=146**	**BAT N=73**		
	%	**%**	**%**	**%**	**%**	
Infections and infestations						
Urinary Tract infections[1]	9.0	5.3	14.4	6.8	11.6	Very common
Herpes zoster[1]	1.9	0.7	4.8	0	3.3	Common
Blood and lymphatic system disorders						
Anemia[2]						
CTCAE [3] Grade 4 (<6.5g/dL)	11.0	2.6	8.2	9.6	9.6	Common
CTCAE Grade 3 (<8.0 – 6.5g/dL)	31.6	12.6	30.1	11.0	30.9	Very common
Any CTCAE Grade	81.9	41.7	81.5	49.3	81.7	Very common

Thrombocytopenia[2]						
CTCAE Grade 4 (<25,000/mm^3)	3.9	0	2.1	2.7	3.0	Common
CTCAE Grade 3 (50,000 – 25,000/mm^3)	9.0	1.3	6.2	4.1	7.6	Common
Any CTCAE Grade	68.4	19.2	66.4	26.0	67.4	Very common
Neutropenia[2]						
CTCAE Grade 4 (<500/mm^3)	1.9	1.3	2.7	1.4	2.3	Common
CTCAE Grade 3 (<1000 – 500/mm^3)	4.5	0.7	3.4	0	4.0	Common
Any CTCAE Grade	18.1	4.0	12.3	8.2	15.3	Very Common
Metabolism and nutrition disorders						
Weight gain[1]	7.1	1.3	9.6	0	8.3	Common
Hypercholesterolemia [2,4] Any CTCAE Grade	17.4	0.7	15.8	6.8	16.6	Very common
Nervous system disorders						
Dizziness[1]	18.1	7.3	9.6	8.2	14.0	Very common
Headache[1]	14.8	5.3	10.3	4.1	12.6	Very common
Gastrointestinal disorders						
Flatulence[1]	5.2	0.7	1.4	0	3.3	Common
ADRs and CTCAE Grade	**INCB 18424-351**		**CINC424A2352**		**Total Ruxolitinib N=301**	**Frequency category**
	Ruxolitinib N=155	**Placebo N=151**	**Ruxolitinib N=146**	**BAT N=73**		
	%	**%**	**%**	**%**	**%**	
Hepatobiliary disorders						
Raised alanine aminotransferase[2, 5]						Common
CTCAE Grade 3 (>5x – 20 x ULN)	1.3	0	1.4	0	1.3	Common
Any CTCAE Grade	27.1	7.9	25.3	6.8	26.2	Very common
Raised aspartate aminotransferase[2,5]						Very common
Any CTCAE Grade	18.1	6.6	19.2	2.7	18.6	
Skin and subcutaneous tissue disorders						

Bruising[1]	23.2	14.6	13.7	5.5	18.6	Very common

[1] Frequency is based on adverse event data.
[2] Frequency is based on laboratory values.
-A subject with multiple occurrences of an ADR is counted only once in that ADR category.
-ADRs reported are on treatment or up to 28 days post treatment end date.
[3] CTCAE Version 3.0;
Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life-threatening or disabling.
[4] In Phase III clinical studies no CTCAE Grade 3 or 4 hypercholesterolemia was observed.
[5] In Phase III clinical studies no CTCAE Grade 4 raised ALT was observed and no CTCAE Grade 3 or 4 raised AST was observed.
ULN=upper limit of normal
-A subject with multiple occurrences of an ADR is counted only once in that ADR category.
-ADRs reported are on treatment or up to 28 days post treatment end date.

Infectious complications

Serious bacterial, mycobacterial, fungal and viral infections may occur. Therefore active serious infections should have resolved before starting therapy with ruxolitinib. Patients receiving ruxolitinib should be observed for signs and symptoms of infection and treatment should be initiated promptly. Few anecdotal reports have reported infectious complications including, reactivation of latent virus infections, Progressive multifocal leukoencephalopathy in a patient with myelofibrosis, Herpes Zoster (see also section 6.1).

Deaths and other serious adverse events in the MF clinical trials

In the Phase III population, there were 34 deaths in total, 27 of which were on-treatment deaths: 20 deaths in study Comfort I (9 in the ruxolitinib group, 11 in the placebo group) and 7 deaths in study Comfort II (4 in the ruxolitinib group, 3 in the BAT group). The reasons for death (infections, intestinal perforation, disease progression and events probably due to disease progression, bleedings events) were similar in the ruxolitinib and the placebo groups. In the ruxolitinib-treated Phase III population, the overall frequency of SAEs was 28.9%. This frequency was similar across both studies. The most frequently reported SAEs in ruxolitinib-treated patients were anemia (4.0%) and pneumonia (3.7%). Pneumonia was the only SAE that was reported in more than 5% in any treatment group (ruxolitinib group with 6.5% and BAT group with 5.5%). When evaluating all lower respiratory tract infection AEs grouped by MedDRA higher level group term (MedDRA: Medical Dictionary for Regulatory Activities), there was no appreciable difference across the arms of the studies: ruxolitinib 10.3% vs. placebo 7.3%; ruxolitinib 13.1% vs. BAT 18%). Most other SAEs were reported in three patients or fewer in any group, with the following exceptions: in the placebo group, abdominal pain was reported as an SAE in six patients (4.0%), and splenic infarction in four patients (2.6%); in the ruxolitinib-treated patients, fatigue, gastrointestinal hemorrhage and pyrexia were reported in four patients (1.3%) each.

2.2.10 Warnings and precautions

Thrombocytopenia, Anemia and Neutropenia

Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia.. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.

Risk of Infection

Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly.

Tuberculosis

Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed.

For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination.

PML

Progressive multifocal leukoencephalopathy (PML) has occurred with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate.

Herpes Zoster

Advice patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected.

Hepatitis B

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi 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.

Symptom exacerbation following interruption or discontinuation of treatment with Jakafi

Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with myelofibrosis have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5)*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations.

Lipid Elevations

Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

2.2.11 Contraindications

Hypersensitivity to the active substance or any of the excipients.

2.2.12 Combination with other drugs

No information exists for combining ruxolitinib with other standard MF-therapies and this is discouraged outside a clinical trial. No data are available regarding interactions of ruxolitinib with hematopoietic stimulatory drugs such as erythropoietin and thrombopoietin agents. However potential interactions with these agents are possible based on their signaling through the JAK/STAT pathway.

2.2.13 Dosage and administration

The recommended starting dose of ruxolitinib is 15 mg given orally twice daily for MF patients with a platelet count between 100 x 10^9/L and 200 x 10^9/L and 20 mg twice daily for MF patients with a platelet count of >200 x 10^9/L. There is limited information to recommend a starting dose for patients with platelet counts between 50 x 10^9/L and 100 x 10^9/L. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously. Doses may be titrated based on safety and efficacy. Treatment should be interrupted for platelet counts less than 50 x 10^9/L or ANC less than 0.5 x 10^9/L. After recovery of platelet and neutrophil counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of blood cell counts.

Dose reductions should be considered if the platelet counts decreases below 100 x 10^9/L with the goal of avoiding dose interruptions for thrombocytopenia.
If efficacy is considered insufficient and platelet and neutrophil counts are adequate, doses may be increased by a maximum of 5 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

The maximum dose of ruxolitinib is 25 mg twice daily. If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose. Treatment may be continued as long as the benefit: risk remains positive.

2.2.14 Special populations

Pregnancy

Risk Summary: There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There was no evidence of teratogenicity. However, decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal

survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily).

Nursing mothers

It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

The safety and effectiveness of Jakafi in pediatric patients have not been established.

Geriatric Use

Of the total number of patients with myelofibrosis in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients.Renal Impairment - The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [CrCl 72-164 mL/min (N=8)] and in subjects with mild [CrCl 53-83 mL/min (N=8)], moderate [CrCl 38-57 mL/min (N=8)], or severe renal impairment [CrCl 15-51 mL/min (N=8)]. Eight (8) additional subjects with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamics marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolite exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia Vera and moderate (CrCl 30-59 mL/min) or severe renal impairment (CrCl 15-29 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended.

Hepatic Impairment
The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild [Child-Pugh A (N=8)], moderate [Child-Pugh B (N=8)], or severe hepatic impairment [Child-Pugh C (N=8)]. The mean AUC for ruxolitinib was increased by 87%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal

hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamics marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia Vera and hepatic impairment.

2.2.15 Drug Interactions

Drugs that inhibit or induce cytochrome P450 enzymes: Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9.

CYP3A4 inhibitors: The C_{max} and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction.

Fluconazole: The AUC of ruxolitinib is predicted to increase by approximately 100% to 300% following concomitant administration with the combined CYP3A4 and CYP2C9 inhibitor fluconazole at doses of 100 mg to 400 mg once daily, respectively. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily.

CYP3A4 inducers: The C_{max} and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy.

2.2.16 Over-dosage

There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of ruxolitinib.

2.2.17 Post-marketing experience

Ruxolitinib has been granted Marketing Authorization Approval in the USA for PV not responding to hydroxyurea, intermediate or high-risk myelofibrosis, including PMF, post– polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis, and in Canada marketing authorization was granted in June 2012 for the

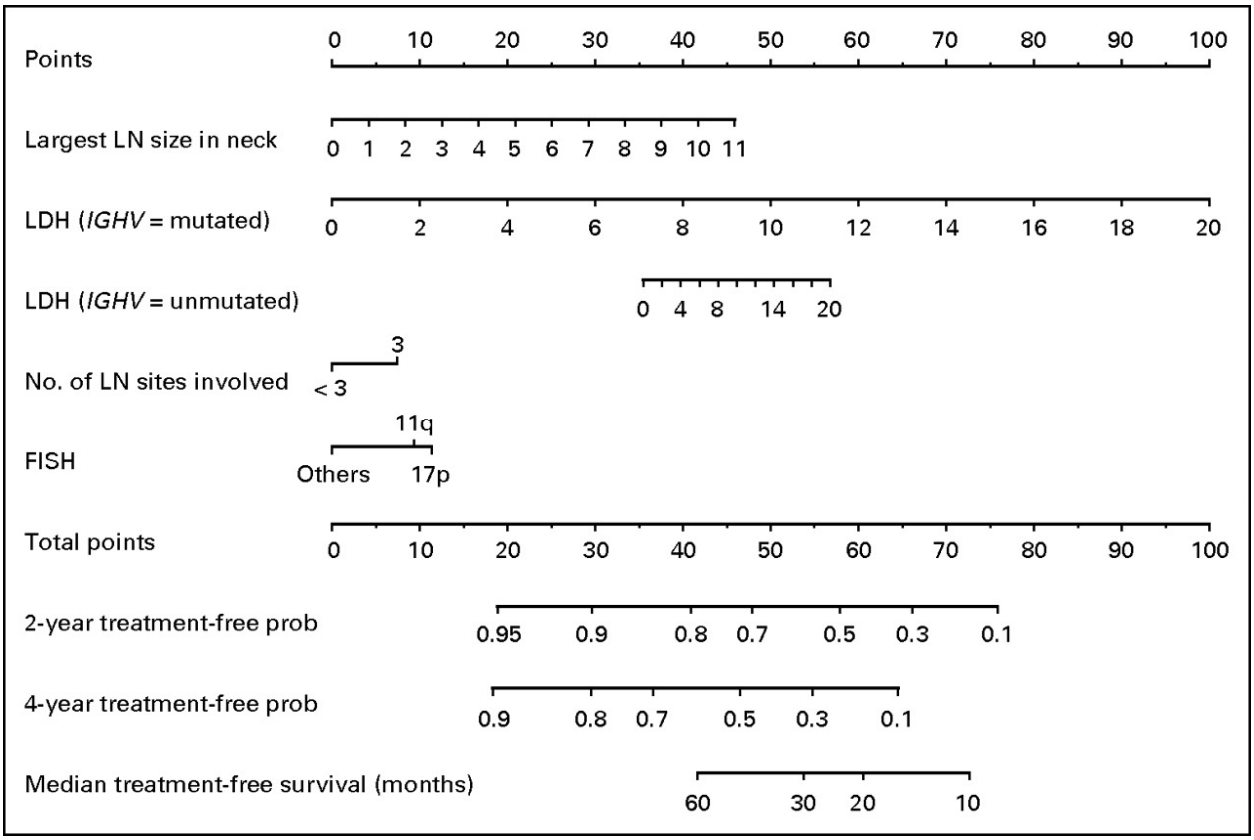
indication of splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), postpolycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis. In the EU, the CHMP has granted a positive opinion in April 2012, and granted approval for the treatment of disease related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis, or post essential thrombocythemia myelofibrosis in August 2012. Regulatory review is ongoing in other countries. The product is currently marketed in the USA, Canada, and the European Union under the brand name JAKAFI® (USA) and JAKAVI® (Canada and EU).

3.0 PATIENT SELECTION

3.1 Eligibility

Patients with high-risk (Figure 1), previously untreated CLL/SLL that do not require therapeutic intervention according to the IWCLL guidelines, based on the Rai and Binet staging systems(Table 3), but are likely to require treatment within ≤ 4 years if remain untreated, according to the below nomogram (Figure 1) will be eligible to enroll onto the study.

Figure 1. Nomogram for time to first treatment (Wierda et al., 2011)



Nomogram used by totaling points identified at top scale for each of four independent variables. Point score for lactate dehydrogenase (LDH) identified based on *IGHV* mutation status. This summed point score then identified on total point scale to identify 2- and 4-year treatment-free probability (prob) and estimate treatment-free survival. Fluorescent in situ hybridization (FISH) was categorized by Dohner hierarchic categorization. LN, lymph node.

This nomogram provides a visual depiction of the relative contribution of each prognostic factor to the total point score and, thus, the weight of factors regarding risk for requiring first treatment. The formula for calculating the total point score is as follows: [I(No. of lymph node sites involved = 3) × 7.370 + I(FISH = 11q del) × 9.312 + I(FISH = 17p del) × 11.285 + (diameter of largest cervical lymph node in cm) × 4.172 + (LDH/100) × I([*IGHV* gene = mutated] × 5.000 + (LDH ÷ 100) × I(*IGHV* gene = unmutated) × 1.065] + 35.467. The indicator function (I) is equal to 1 if the statement in the parentheses is true and is equal to 0 otherwise. The total point scores ranged from 0 to 87.4 points, with a median of 21.0.

Table 3. IWCLL recommendations for the treatment of CLL/SLL (Hallek et al., 2008)

	General practice/Clinical trial	
Treat with Rai stage 0	NGI	RQ
Treat with Binet stage A	NGI	RQ
Treat with Binet stage B or Rai stage I or Rai stage II	Possible	Possible
Treat with Binet stage C or Rai stage III or Rai stage IV	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	NGI	RQ

NGI, indicates not generally indicated unless the patients shows features of disease progression or disease transformation; and RQ, research question.

3.1.1 Inclusion criteria

1) Subjects who are able to understand and sign an informed consent document.
2) Subjects 18 years of age or older.
3) Subjects must be diagnosed with CLL/SLL and do not meet the IWCLL criteria for treatment (Hallek et al., 2008).
4) Patients should be previously untreated or have only been treated with single agent ibrutinib therapy for a period of < 3 months and were deemed ibrutinib intolerant.
5) Patients whose expected time to CLL/SLL treatment, according to our nomogram (Figure 1), is four years of less.
6) Subjects with hemoglobin values at the screening visit equal to or greater than 12.0 g/dL.
7) Subjects with a platelet count of at least 100 $x10^9$/L at the screening visit.
8) Subjects with an absolute neutrophil count (ANC) of equal to or higher than 0.5 $x10^9$/L at the screening visit.

9) Subject who are willing to undergo a bone marrow aspiration and biopsy and CT scan for disease burden assessment.
10) Patient who are capable to return to MDACC for follow-up.
11) Subjects with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
12) Patient must be capable of swallowing the Ruxolotinib capsules (tablets).

3.1.2 Exclusion criteria

1) Females who are pregnant or are currently breastfeeding.
2) Subjects of childbearing potential who are unwilling to take appropriate precautions (Throughout the study from screening, including 30 days after discontinuation of the study drug) to avoid becoming pregnant or fathering a child.
   - Females of non-childbearing potential are defined as women who (a) are equal to or greater than 55 years of age with history of amenorrhea for 1 year, OR (b) are surgically sterile for at least 3 months.
   - For females of childbearing potential, or for males, appropriate precautions are those that are at least 99% effective in preventing the occurrence of pregnancy. These methods should be communicated to the subjects and their understanding confirmed:
     - Double barrier methods
     - Condom with spermicide in conjunction with use of an intrauterine device (IUD)
     - condom with spermicide in conjunction with use of a diaphragm
     - Oral, injectable, or implanted contraceptives
     - Tubal ligation or vasectomy (surgical sterilization)
3) Subjects with recent history of inadequate bone marrow reserve as demonstrated by previous transfusions except for acute blood loss (e.g. surgery) in the month prior to screening.
4) Subjects with inadequate liver or renal function at screening and baseline visits:
   - Alanine aminotransferase (ALT) > 2.5x ULN.
   - Modification of Diet in Renal Disease (MDRD) calculated GFR < 30 mL/min
5) Subjects with active uncontrolled infection or who are HIV positive (Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered controlled).
6) Subjects with history of or a current invasive malignancy over the past 5 years except for treated ba+
7) sal or squamous carcinomas of the skin completely resected. Other completely resected cancers less than 5 years may be considered after PI review.
7) Subjects with clinically significant uncontrolled cardiac disease.
8) Subjects being treated concurrently with any prohibited medications, including investigational medication, rifampin, St. John's wort, and potent CYP3A4 inhibitors, Excluding ketoconazole) unless continuation of such medications are determined by the investigator to be in the best interest of the patient (as detailed in protocol section 2.2.15 and Table 3).

9) Subjects who have previously received JAK inhibitor therapy. ++
10) Subjects with active alcohol or drug addiction that would interfere with their ability to Comply with the study requirements.
11) Subjects with any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the subject or compliance with the protocol.
12) Subjects who have unknown transfusion history.
13) Patients who cannot comply with the study requirements.

4.0 TREATMENT PLAN

4.1 Administration of Study Drug

Ruxolitinib will be administered twice daily (bid), approximately 12 hours apart. The starting dose will be 20 mg bid for patients with a platelet count of ≥ 200 $x10^9$/L (dose level 1) and 15 mg bid for patients with a platelet count of ≥ 100 $x10^9$/L and ≤ 200 $x10^9$/L (dose level -1). The starting dose for patients a hemoglobin level of 12 -13 g/dL will be 10 mg bid (dose level -2). Dose adjustment (de-escalation) will be done in accordance with the scheme outlined in Table 4. Tablets will be taken without regard to food on an outpatient basis. Vomited doses can be made up, if the person vomits within 30 minutes after taking ruxolitinib. If the person vomits after 30 minutes upon taking ruxolitinib, the person may wait to take it when it is time to take the next dose.

Dose adjustments are required for protocol-specified clinically significant ruxolitinib-related adverse events (AEs) of Grade 3 or Grade 4 severity, declining platelet counts, declining absolute neutrophil counts (ANC) and declining hemoglobin levels (Table 4 and Section 5). Discontinuation of Ruxolitinib should be gradual to avoid "ruxolitinib withdrawal syndrome".

Table 4. Dose (mg) adjustment schema

b.i.d	Dose (b.i.d.)
1	20
-1	15
-2	10
-3	5

4.2 Treatment Compliance

Subjects will return all bottles of unopened, empty, and opened/partially used study drug at study visits. Investigative site staff will perform a count of returned pills to assess compliance, and this information will be reported on the Case Report Form (CRF). Study drug which is returned will be destroyed in accordance with the site's drug destruction policy. A standard institutionally approved diary may be issued to subjects.

4.3 Duration of Treatment and Subject Participation

Subjects will continue treatment as long as clinically indicated as judged by the Principal Investigator (PI) of the study or the attending physician for up to 3 years. Treatment beyond 3 years may be permitted after discussion with the PI. The discussion should be documented in the subject's medical record.

4.4 Patient Assessments

Patients will be presented with the informed consent at screening. They will fill out the Brief Fatigue Inventory (BFI) and the MD Anderson Symptom Inventory (MDSI) at each visit to MDA starting on Day 1. Patients will be seen at MDA during the screening period (-15-1 day), Day 1, Day 15 ± 7 days, Month 2 ± 7days, Month 3 ± 7 days, Month 6 ± 2 months and Month 8 ± 2 months, 10, 12, and so on. Every clinic visit to MDACC will include a routine physical examination, Brief Fatigue Inventory (BFI) and MD Anderson Symptom Inventory (MDSI) questionnaires and standard laboratory tests including CBC with differential and, plts, chemistries to include creatinine and ALT, Immunoglobulin levels (IgG, IgA and IgM), T cell counts and Beta-2 microglobulin (b2M).

If you can become pregnant, blood (about 1 teaspoon) and/or urine will be collected for a pregnancy test.

Correlative studies will be conducted to understand changes in the immunological and cytokine/chemokine pathways in CLL in response to ruxolitinib. Correlative studies will only be performed at MDACC visits: Day 1 (pre-dose), Month 3 ± 7 days, and Month 6 ± 2 mos. or as requested by the PI for specific patients with unusual response or unusual clinical presentation. Complete blood counts should be monitored every 2-4 weeks at MDACC or by the patient's local physician until counts are stabilized.

After month 8 ± 2 mos the patient is required to have a physical exam, hematology and chemistry every 2 months ± 2 mos. (Month 10, 12, and so on.) Every other visit may be conducted by the patient's local physician if more convenient for the patient.

Follow-Up

About 30 days after your last dose of ruxolotinib, blood (about 2 teaspoons) will be drawn for routine tests.

5.0 DOSING DELAYS/ DOSE MODIFICATIONS

5.1 Concomitant Use with Strong CYP3A4 Inhibitors or Fluconazole

Modify the dose of Jakafi when given concomitantly with strong CYP3A4 inhibitors (such as but not limited to boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and fluconazole doses of less than or equal to 200 mg as follows .

5.2 Dosing Delays

Up to a one month delay in the next dosing of Ruxolitinib, elected to be changed due to clinical side effects or laboratory abnormalities, is allowed.

5.3 Dose Modification of Ruxolitinib in Different Clinical Scenarios

Table 5. Dose modification for drug interactions

Patients on concomitant strong CYP3A4 inhibitors or fluconazole doses of less than or equal to 200 mg	**Recommended Dose Modification**
Starting Dose for Patients with Myelofibrosis with a platelet count:	
• Greater than or equal to 100 X 10^9/L	10 mg twice daily
• 50 X 10^9/L to less than 100 X 10^9/L	5 mg once daily
Starting Dose for Patients with Polycythemia Vera	5 mg twice daily
All Patients on a Stable Dose of:	
• Greater than or equal to 10 mg twice daily	Decrease dose by 50% (round up to the closest available tablet strength)
• 5 mg twice daily	5 mg once daily
• 5 mg once daily	Avoid strong CYP3A4 inhibitor or fluconazole treatment or interrupt Jakafi treatment for the duration of strong CYP3A4 inhibitor or fluconazole use

Avoid the use of fluconazole doses of greater than 200 mg daily concomitantly with Jakafi. Additional dose modifications should be made with careful monitoring of safety and efficacy.

5.4 Renal Function Impairment

Modify the dose of Jakafi accordingly in patients with moderate or severe renal function impairment.

Table 6. Dosing for renal function impairment

Renal Impairment Status	Platelet Count	Recommended Starting Dosage
Patients with Myelofibrosis Moderate (CrCl 30–59 mL/min) or Severe (CrCl 15–29 mL/min)	Greater than 150 X 10^9/L	No dose modification needed
	100 X 10^9/L - 150 X 10^9/L	10 mg twice daily
	50 - less than 100 X 10^9/L	5 mg daily
	Less than 50 X 10^9/L	Avoid use [*see Use in Specific Populations (8.6)*]
Patients with Polycythemia Vera Moderate (CrCl 30-59 mL/min) or Severe (CrCl 15-29 mL/min)	Any	5 mg twice daily

5.4.1 Patients on dialysis

The recommended starting dose for patients with myelofibrosis with end stage renal disease on dialysis is 15 mg once after a dialysis session for patients with a platelet count between 100 X 10^9/L and 200 X 10^9/L or 20 mg for patients with a platelet count of greater than 200 X 10^9/L. The recommended starting dose for patients with polycythemia Vera with end stage renal disease on dialysis is 10 mg. Additional dose modifications should be made with frequent monitoring of safety and efficacy. Avoid use of Jakafi in patients with end stage renal disease (CrCl less than 15 mL/min) not requiring dialysis.

5.5 Hepatic Impairment

The dose of Jakafi should be reduced in patients with hepatic impairment.

Table 7. Dosing for hepatic impairment

Hepatic Impairment Status	Platelet Count	Recommended Starting Dosage

Patients with Myelofibrosis Mild, Moderate, or Severe (Child- Pugh categories A, B, C)	Greater than 150 X 10^9/L	No dose modification needed
	100 X 10^9/L - 150 X 10^9/L	10 mg twice daily
	50 - less than 100 X 10^9/L	5 mg daily
	Less than 50 X 10^9/L	Avoid use [*see Use in Specific Populations (8.6)*]
Patients with Polycythemia Vera Mild, Moderate, or Severe (Child- Pugh categories A, B, C)	Any	5 mg twice daily

6.0 AGENT FORMULATION AND PROCUREMENT

Formulation: Ruxolitinib (Jakafi®) is commercially available in the US in 5, 10, 15, 20, and 25 mg strength tablets. The tablet contains the active ingredient and may include the following commonly used excipients: microcrystalline cellulose, lactose, stearic acid, magnesium stearate, colloidal silicone dioxide, sodium starch glycolate, Povidone, and hydroxyl propyl cellulose. All excipients are of US and EuPh compendial grade.

The 5 mg (free base equivalent) and 25 mg (free base equivalent) tablets are packaged in HDPE bottles. All bottles of Incyte investigational product contain the following language: “Caution: New Drug-Limited by Federal Law to Investigational Use.” The clinical supply for investigational use is the 5 mg tablet.

Storage and Stability: Ruxolitinib has been shown to be stable for up to 6 months at 40 degrees C and up to 24 months when stored at 25 degrees C.

Compatibility: Ruxolitinib may be taken either with food or without food

Handling: Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Availability: Ruxolitinib will be supplied free-of-charge by Incyte Corp.

7.0 CORRELATIVE/ SPECIAL STUDIES

Patients' plasma samples and peripheral blood cells will be obtained prior to and approximately 3 and 6 months of treatment, or as requested by PI for specific patients with unusual response or unusual clinical presentation.

Those samples will be stored at -20°C in the P.I.'s laboratory, using appropriate de-identifiers, and plasma cytokine levels (such as IL-1, IL-6, and IFNs (Verstovsek et al., 2008-0874) will be measured and changes in B-cell receptor signaling pathways will be assessed using standard technology.

8.0 PATIENT EVALUATION

Patients will be evaluated in accordance with our standard of care. Every clinic visit to MDACC will include a routine physical examination and standard laboratory tests including CBC with differential and, plts, chemestries to include creatinine and ALT, Immunoglobulin levels (IgG, IgA and IgM), T cell counts and Beta-2 microglobulin (b2M). Correlative studies will be conducted to understand changes in the immunological and cytokine/chemokine pathways in CLL in response to ruxolitinib. Correlative studies will only be performed at MDACC at visits: Day 1 (pre-dose), Month 3 $\pm$ 7 days, and Month 6 $\pm$ 2 mos., or as requested by the PI for specific patients with unusual response or unusual clinical presentation. Complete blood counts should be monitored every 2-4 weeks at MDACC or by the patients local physician until counts are stabilized. After month 8 $\pm$ 2 mos., the patient is required to have a physical exam, hematology and chemistry every 2 months $\pm$ 2 mos, every other visit may be conducted by the patient's local physician if more convenient for the patient. A bone marrow aspiration and biopsy and whole body CT scan will be completed at screening (-15-1 day) and at 6 months $\pm$ 2 months of treatments (as per standard of care for CLL/SLL) will be performed at MDACC. We will use the CLL/SLL module of the MD Anderson Symptom Inventory and Brief Fatigue Inventory (measuring symptoms "at their worst") of common symptoms associated with CLL/SLL at every visit to MDACC.

8.1 Outside Physician Participation during Treatment

1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix H)
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
4. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

5. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.
6. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.
7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.
8. Patient will have a physical exam every 1-2 months.

Patients are allowed to have hematology and biochemistry tests performed in outside laboratory facilities. Laboratory results will be obtained by the research staff assigned to this study. The PI or treating physician listed on the delegation of authority log will review outside labs and determined the clinical significance of these labs. The physician will sign and date the outside lab result.

Follow-ups and disease burden assessments will only be performed by the MD Anderson Cancer Center team. Patients must be followed for SAE/AEs until at least 30 days after the last dose of study drug. SAE/AE will be assessed on their next visit to the leukemia clinic at MDACC. Participant will be removed from the protocol study after the 30-day post-treatment visit/assessment.

All protocol specific data will be entered into PDMS/CORe.

8.2 Symptom Score Assessment

After signing the informed consent, patients will fill out the Brief Fatigue Inventory (BFI) (Appendix E) and the MD Anderson Symptom Inventory (MDSI) (Appendix F). The patients will fill out the BFI and MDSI forms at Day 1 and every visit to MDACC. These time points were chosen based on our symptom control study of patents with CLL (protocol 2013-0044).

8.3 Disease Response Assessment

Assessment of clinical response will be conducted in accordance with our standard of care (physical examination, CBC, a bone marrow aspiration, and a whole body CT scan to be done at screening and 6 $\pm$ 2 months into treatment).

The IWCLL response criteria (Hallek et al., 2008) (Table 8) will be used to assess disease response. A bone marrow aspiration, a whole body CT scan is to be done at screening and 6 $\pm$ 2 months into treatment to further assess response. If a 20% reduction in tumor burden is observed at 6 $\pm$ 2 months, Treatment will be continued.

Table 8. Response definition after treatment for patients with CLL/'SLL, using the parameters of Tables 1 and 3

Parameter	CR*	PR*	PD*
Group A			
Lymphadenopathy‡	None > 1.5 cm	Decrease ≥ 50%	Increase ≥ 50%
Hepatomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B			
Platelet count	> 100 000/μL	> 100 000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL/SLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL/SLL
Neutrophils‡	> 1500/μL	> 1500/μL or > 50% improvement over baseline	

Group A criteria define the tumor load, group B criteria define the function of the hematopoietic system (or marrow).
* CR (complete remission): all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR (partial remission): at least two of the criteria of group A plus one of the criteria of group B have to be met; SD is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above criteria of group A or group B has to be met.

9.0 RESPONSE CRITERIA

Response criteria including tumor mass reduction will be assessed at approximately six to eight months by using physical examination, laboratory data, bone marrow analysis (including cytogenetic and, if indicated, molecular analysis), and CT scan analysis.

9.1 Disease Response Criteria

Clinical response will be assessed based on physical examination, CBC, a bone marrow aspiration, a whole body CT scan to be done at screening and 6 ± 2 months in accordance with the IWCLL guidelines (Hallek et al., 2008) as outlined in Table 8. If a 20% reduction in tumor burden is observed at 6 ± 2 months, Treatment will be continued as long as a CR, PR or at least a 20% reduction in tumor mass is achieved and sustained.

10.0 CRITERIA FOR REMOVAL FROM THE STUDY

Patients will be removed from the study for the following reasons:

1. Pattern of noncompliance.
2. Toxicity (grade 3 or 4) inducing clinical symptoms necessitating red blood cell or platelet transfusions and not alleviated after dose adjustment.
3. Disease progression that require another therapeutic intervention (an increase in peripheral blood lymphocyte count is expected. If needed anti-CD20 antibody treatment (Rituximab or Ofatumumab) or leukopheresis are allowed).
4. Lack of response (a reduction of 20% of tumor mass or PR) at 6 ± 2 months.
5. Unexpected events (medical or other) that would prevent the patient from staying on study.
6. Patient's or physician's choice. Compliance will be assessed by the P.I. based on the drug accountability documented by the site staff and monitored by the designee. The objective is 100% compliance and the P.I. and his staff will evaluate compliance at each visit, and take appropriate steps to optimize compliance. For the purpose of subgroup analyses, subjects with at least 80% compliance over the total duration of dosing from the first day of dosing to the analysis of the study will be considered to be compliant.

11.0 STATISTICAL CONSIDERATIONS

The study will be conducted at MDACC only. The primary endpoint will assess the clinical response (CR, PR, and a 20% reduction in tumor mass as assessed by a body scan and bone marrow aspiration/biopsy) at 6 ± 2 months after initiation of therapy.

We will incorporate an informal futility analysis when half of the total patients have reached 6 ± 2 months after initiation to assess whether the average change in the tumor mass score is less than zero (calculated as the score at enrollment minus the score at six months). If the average at this time is less than zero, the trial will be stopped early.

Because no treatment is the standard of care for these patients, we will routinely analyze the outcome of our Ruxolitinib-treated patients at a 6 ±2 month interval and compare their clinical outcome to that of patient who elected to receive no treatment.

Table 9 shows the probability of stopping early under several different scenarios, as well as how the overall power is for the primary analysis is affected by early stopping. The operating characteristics were produced in R version 2.13.0 by simulating 5000 trials with 17 patients at the interim and 34 patients at the end of the trial, accounting for a 15% drop out rate. The simulations stop early if the average change at 6 months is less than zero, and formally tests whether the change is not equal to zero at the final analysis using a paired *t*-test.

Table 9. Operating characteristics

True tumor burden difference (baseline score minus score at 6 months)	True SD of the Difference	Prob(Stop Early)	Power for Final Analysis
-1	2	0.9818	0.0026
0	2	0.5068	0.0218
1	2	0.0202	0.8064
2	2	0.0000	0.9998
-1	4	0.8398	0.0014
0	4	0.4958	0.0274
1	4	0.1584	0.2876
2	4	0.0198	0.8074

For primary analysis, the paired t test will be used to evaluate the changes of tumor burden from baseline to 6 ± 2 months after initiation of therapy. Response rate will be estimated with 95% confidence interval. Patients who drop out early will be counted as non-responders. The Kaplan-Meier method will be used to estimate time to next treatment, and will compared to our historical data (Wierda et al., 2011) using Cox proportional hazards model, adjusting for effects of covariates. If necessary and applicable, appropriate methods such as propensity score matching will be used to match the patients of this study with the historical data to reduce comparison bias.

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median and range. Categorical variables will be tabulated by

frequencies and the corresponding percentages. The Fisher's exact test or logistic regression analysis will be used for any binary outcomes. Statistical t-tests or Wilcoxon rank sum tests will be used to compare continuous variables. Longitudinal analysis may be used to model the change in tumor burden.

A Toxicity/Efficacy Summary will be submitted to the IND Office Medical Affairs and Safety Group, after the first five evaluable subjects complete 6 to 8 months from treatment initiation, and every five evaluable subjects thereafter.

11.1 Toxicity monitoring Rule

Bayesian sequential monitoring (1995) will be employed to perform interim safety monitoring targeting a grade 3 and 4 toxicity rate due to the drug of not more than 30% by 3 months. Patients will be monitored in cohorts of 5. Accrual will be stopped early if Pr [prob(toxicity) > 0.30 | data] > 0.96. That is, if we determine that there is a greater than 96% chance that the toxicity rate is greater than 30%, then the study will be stopped. We assume a beta (0.6, 1.4) prior distribution for the toxicity rate, which has a mean of 0.3 corresponding to the 30% target toxicity rate. The historical prior is based on a sample of (300, 700). Table 11 depicts stopping criteria. Stopping conditions corresponding to this probability criterion are to terminate accrual if:

Table 10. Toxicity monitoring rules and stopping conditions

If there are this many (or more) patients with ruxolitinib-related, grade 3 or 4 clinically significant toxicity	Stop the study if this many (or fewer) patients
4	5
6	10
9	15
11	20
12	25
14	30
16	35
18	40

This stopping rule was chosen to assure that the probability that this portion of the study will stop early would be approximately 11% if the true rate of toxicity was no more than 30%. The operating characteristics of this rule were generated by the Biostatistics Department's Multc Lean Desktop program (version 1.2.0) and are shown in Table 11.

Table 11. Operating characteristics for toxicity stopping rule

If the true grade toxicity rate is…	Early Stopping Probability	Achieved Sample Size 25th, 50th, 75th percentiles		
0.1	0.0006	40	40	40
0.2	0.0127	40	40	40
0.3	0.1073	40	40	40
0.4	0.4311	20	40	40
0.5	0.8225	5	20	30
0.6	0.9808	5	10	15

11.2 Trial Conduct

The PI or designee will be responsible for assessing the toxicity monitoring and early stopping rules. The biostatistical collaborators will be available for any assistance.

Protocol specific data and adverse events will be entered into PDMS/CORe. PDMS/CORe will be used as the electronic case report form for this protocol.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

12.0 REPORTING REQUIREMENTS

Adverse events will be reported in accordance with the Leukemia-specific Adverse Event Recording and Reporting Guidelines (Appendix G). Adverse events will only be collected up to 30 days after the last dose of ruxolitinib. Adverse event reporting will be as per the NCI version 4 criteria and the MDACC Leukemia Specific Adverse Event Recording and Reporting Guidelines.

Adverse events will be recorded on the Adverse Event Record (AER) for each patient after every protocol visit. The Principal Investigator will sign and date the Adverse Event record for every patient after every protocol visit. Following signature, the Adverse Event Record will be used as source documentation for the adverse events for attribution.

Concomitant medications will be captured in the electronic medical record and not needed in the data capture.

12.1 Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting protocol intervention, up to 30 days after the last dose of ruxolitinib, even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)

2. its relationship to the study drug(s) (suspected/not suspected)

3. its duration (start and end dates or if continuing at final exam)

4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

5. whether it constitutes a serious adverse event (SAE)

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] (Appendix C)..

Adverse events will be reported in accordance with the Leukemia-specific Adverse Event Recording and Reporting Guidelines (Appendix G), and as per the NCI CTCAE criteria version 4.

Only unexpected AEs will be recorded in the Case Report Form (CRF). The PI or designee will be responsible for assigning attribution of adverse events to the study agent.

The Principal Investigator will sign and date the PDMS Case Report Form toxicity pages per each patient approximately every 3 months. Following signature, the Case Report Form will be used as source documentation for the adverse events for attribution.

Appendix G encloses the guidelines dated 06/24/16.

12.2 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to
- conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- Reporting to FDA:
- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.
- It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

- **Incyte Corporation**: IncytePhVOpsIST@incyte.com for e-mail transmission of individual SAE reports.
- **Safety Contacts:** Kathy Lenard Roberts, Exec. Dir, Incyte Pharmacovigilance Phone: 302-498-6727, Fax:302-425-2780
- **Safety Contacts:** Kathy Lenard Roberts, Exec. Dir, Incyte Pharmacovigilance Phone: 302-498-6727, Fax:302-425-2780
- **Pharmacovigilance & Drug Safety:** Robert Livingston, MD, Vice President, Incyte, Phone: 302-498-7098, Fax: 302-425-2780

13.0 REFERENCES

Badoux X, Bueso-Ramos C, Harris D, et al. Cross-talk between chronic lymphocytic leukemia cells and bone marrow endothelial cells: role of signal transducer and activator of transcription 3. *Hum Pathol*. 2011;42:1989-2000.

Barsevick AM, Cleeland CS, Manning DC, et al. ASCPRO recommendations for the assessment of fatigue as an outcome in clinical trials. *J Pain Symptom Manage.* 2010;39:1086-1099.

Burger JA. Chemokines and chemokine receptors in chronic lymphocytic leukemia (CLL): from understanding the basics towards therapeutic targeting. Semin Cancer Biol. 2010;20:424-30.

Collins RJ, Verschuer LA, Harmon BV, et al. Spontaneous programmed death (apoptosis) of B-chronic lymphocytic leukaemia cells following their culture in vitro. *Br J Haematol*. 1989;71(3):343-350.

Dietrich S, Kramer OH, Hahn E, et al. Leflunomide induces apoptosis in fludarabine-resistant and clinically refractory CLL cells. *Clin Cancer Res*. 2012;18:417-431.

Douglas RS, Capocasale RJ, Lamb RJ, Nowell PC, Moore JS. Chronic lymphocytic leukemia B cells are resistant to the apoptotic effects of transforming growth factor-beta. *Blood*. 1997;89:941-947.

Fayad L, Keating MJ, Reuben JM, et al. Interleukin-6 and interleukin-10 levels in chronic lymphocytic leukemia: correlation with phenotypic characteristics and outcome. *Blood.* 2001;97:256-263.

Hallek M, Cheson BD, Catovsky D, et al. International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood.* 2008 Jun 15;111(12):5446-56.

Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur J Haematol.* 2004 Jun;72:381-9.

Ivanenkov YA, Balakin KV, Tkachenko SE. New approaches to the treatment of inflammatory disease : focus on small-molecule inhibitors of signal transduction pathways. *Drugs R D*. 2008;9:397-434.

Kern C, Cornuel JF, Billard C, et al. Involvement of BAFF and APRIL in the resistance to apoptosis of B-CLL through an autocrine pathway. *Blood*. 2004;103:679-688.

Liu Z, Hazan-Halevy I, Harris DM, Li P, et al. STAT-3 activates NF-kappaB in chronic lymphocytic leukemia cells. *Mol Cancer Res.* 2011;9:507-15.

Mahadevan D, Choi J, Cooke L, et al. Gene Expression and Serum Cytokine Profiling of Low Stage CLL Identify WNT/PCP, Flt-3L/Flt-3 and CXCL9/CXCR3 as Regulators of Cell Proliferation, Survival and Migration. *Hum Genomics Proteomics*. 2009;2009:453-634.

Mascarenhas J, Hoffman R. Ruxolitinib: the first FDA approved therapy for the treatment of myelofibrosis. *Clin Cancer Res.* 2012;18:3008-14.

Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer.* 1999;85:1186-96.

Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. *Cancer*, 2007;109:68-76.

Mesa RA, Kantarjian H, Tefferi A, et al. Evaluating the serial use of the Myelofibrosis Symptom Assessment Form for measuring symptomatic improvement: performance in 87 myelofibrosis patients on a JAK1 and JAK2 inhibitor (INCB018424) clinical trial. *Cancer.* 2011;117:4869-77.

Quesada V, Conde L, Villamor N, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. *Nat Genet*. 2012;44(1):47-52.

Rozovski U, Wu JY, Harris DM, et al. Stimulation of the B-cell receptor activates the JAK2/STAT3 signaling pathway in chronic lymphocytic leukemia cells. *Blood* 2014;123:3797-802.

Rozovski U, Hazan-Halevy I, Keating MJ, Estrov Z. Personalized medicine in CLL: current status and future perspectives. *Cancer Lett.* 2014;352:4-14.
Sloan JA, Cella D, Hays RD. Clinical significance of patient-reported questionnaire data: another step toward consensus. *J Clin Epidemiol.* 2005 Dec;58(12):1217-9

Sternberg CN, Molina A, North S, et al. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Ann Oncol.* 2013; 24(4):1017-25.

Verstovsek S, Kantarjian HM, Estrov Z, et al. Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. *Blood.* 2012;120:1202-9.

Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med.* 2010;363:1117-27.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366:799-807.

Vijayakrishnan L, Venkataramanan R, Gulati P. Treating inflammation with the Janus kinase inhibitor CP-690,550. *Trends Pharmacol Sci*. 2011;32:25-34.

Wang L, Lawrence MS, Wan Y, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. *N Engl J Med*. 2011;365:2497-2506.

Wierda WG, O'Brien S, Wang X, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. *J Clin Oncol*. 201;29:4088-95.

Yan XJ, Dozmorov I, Li W, et al. Identification of outcome-correlated cytokine clusters in chronic lymphocytic leukemia. *Blood*. 2011;118:5201-5210.

Yoon JY, Lafarge S, Dawe D, et al. Association of Interleukin-6 and Interleukin-8 with Poor Prognosis in Elderly Chronic Lymphocytic Leukemia Patients. *Leuk Lymphoma*. 2012.