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Protocol Page

Administration of Jakafi (Ruxolitinib) for Symptom Control of Patients with Chronic Lymphocytic Leukemia (CLL): A Phase II Study
2013-0044

Core Protocol Information

Short Title	Administration of Jakafi (Ruxolitinib) for symptom control of patients with CLL: Phase II
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Full Title:	Administration of Jakafi (Ruxolitinib) for Symptom Control of Patients with Chronic Lymphocytic Leukemia (CLL): A Phase II Study
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated 04/13/2016
Version:	10
Submitted by:	Carol L. Ancelet--3/8/2016 11:14:43 AM
OPR Action:	Accepted by: Julie Arevalo -- 4/5/2016 3:55:52 PM

Which Committee will review this protocol?

(•) The Clinical Research Committee - (CRC)

Protocol Body

Jakafi in CLL Symptom Protocol_V8_08 2015.docx

ADMINISTRATION OF JAKAFI (RUXOLITINIB) FOR SYMPTOM CONTROL OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): A PHASE II STUDY

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1.0 OBJECTIVES

1.1 Primary objectives: To estimate the reduction in fatigue as measured by the Brief Fatigue Inventory (BFI) (Appendix G) of patients with CLL who do not require anti-neoplastic therapy according to the IWCLL 2008 recommendations.

1.2 Secondary objectives: To estimate the reduction in other symptoms using the MDASI and to assess disease burden and response by the IWCLL 2008 response criteria.

2.0 BACKGROUND

2.1 Chronic Lymphocytic Leukemia (CLL)

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 CD5 and CD19 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. 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. Fatigue, for example, might at times be so severe that it alone constitutes an indication for treatment, and disease progression is often associated with constitutional B symptoms such as low-grade fever, night sweats, and weight loss (Hallek et al., 2008).

A quality of life (QoL) study of 97 patients with CLL (median age: 68 yr, range: 41-89) compared to age match healthy controls, revealed that CLL patients experience a lower QoL in almost all domains. No differences regarding QoL could be observed between CLL patients who had already received chemotherapy and those who had not. Moreover, female CLL patients were found to have remarkably lower QoL scores in the areas of emotional and social functioning than male patients. CLL patients' QoL improved by effective symptom management and psycho-oncological support (Holzner et al. 2004).

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 recent 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.

No standard therapeutic intervention to control CLL patients' symptoms when chemotherapy is not required is currently available. Because inflammatory cytokine levels are elevated in CLL and contribute to the symptomatology and pathobiology of CLL, and Ruxolitinib was shown to reduce the levels of these cytokines, we hypothesized that Ruxolitinib would alleviate CLL patients' symptoms and reduce tumor burden in this disease.

2.2 Ruxolitinib (Jakafi)

Ruxolitinib ((*R*)-3-(4-(7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate, INCB018424 phosphate, INC424, ruxolitinib phosphate, Jakafi) represents a novel, potent, and selective inhibitor of JAK1 (inhibition concentration 50% [IC50]=3.3 ± 1.2 nM) and JAK2 (IC50=2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (tyrosine kinase 2) (IC50=19 ± 3.2 nM) and JAK3

(IC50=428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several types of cancer and increased proliferation and survival of malignant cells. In particular, this pathway may be dysregulated in the majority of patients with Philadelphia chromosome negative myeloproliferative neoplasms (MPNs, including myelofibrosis [MF] and polycythemia vera [PV]), suggesting that JAK inhibition may be efficacious in these diseases.

Clinical trials were conducted in ET, PV, prostate cancer, and RA. However the largest studies were conducted in MF and most of the clinical data have been accumulated in this disease.

2.2.1 Ruxolitinib mechanism of action

There are four JAK family members, namely JAK1, JAK2, JAK3, and TYK2. The JAKs play an important role in signal transduction following cytokine and growth factor binding to their receptors and aberrant activation of JAKs has been associated with increased malignant cell proliferation and survival. JAKs activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the STATs, a family of important latent transcription factors. In particular, a causal role for JAK2 has recently been suggested for the majority of patients with Philadelphia chromosome negative MPNs. Ruxolitinib represents a novel, potent, and selective inhibitor of JAK1 and JAK2 with modest to marked selectivity against TYK2 and JAK3, respectively, as well as high selectivity against a number of non-JAK kinases (Verstovsek et al., 2012).

2.2.2 Clinical pharmacology

Ten Phase I, five Phase II, and two Phase III clinical studies were conducted to explore the clinical pharmacology of ruxolitinib in healthy volunteers and in patients with MF, ET, PV, subjects with renal or hepatic impairment, prostate cancer, multiple myeloma (MM) or rheumatoid arthritis (RA).

• Oral absorption of ruxolitinib is rapid and nearly complete, with ≥95% absorption indicating high *in vivo* permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentrations are achieved 1-2 h post-dose.
• The effect of food on ruxolitinib exposure is not clinically significant; as a result, the drug may be administered either with or without food.
• Dose proportional exposure is observed between 5 and 200 mg dose range with linear pharmacokinetics (PK).
• Plasma protein binding is approximately 97% *in vitro*. There is moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical

species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier.
• There is >95% [14C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered dose is recovered in urine and feces as unchanged parent drug.
• The mean terminal elimination half-life is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing.
• Metabolism is predominantly via the cytochrome P450 isozyme CYP3A4 to yield oxygenated and subsequent conjugated metabolites.
• Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. *Ex vivo* pharmacokinetic/ pharmacodynamic (PK/PD) analysis indicates that the sum total of 8 active metabolites contribute to 18% of the overall PD activity of ruxolitinib.
• When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%.
• No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers.
• In patients with severe [creatinine clearance (Clcr) < 30 mL/min] and moderate renal impairment (Clcr = 30 -50 mL/min), the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice a day. Patients on hemodialysis should initiate ruxolitinib with a single dose of 15 mg or 20 mg based on platelet counts with subsequent single doses only on hemodialysis days and following each hemodialysis session. Ruxolitinib doses should be titrated based in individual safety and efficacy.
• In patients with mild, moderate or severe hepatic impairment, the recommended starting dose based on platelet count should be reduced by approximately 50% with subsequent dose titration based on individual safety and efficacy.
• Baseline elevations in inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and C-reactive protein (CRP) noted in subjects with MF were associated with constitutional symptoms such as fatigue, pruritus, and night sweats. Decreases were observed in these markers over the 24 weeks of treatment with ruxolitinib, with no evidence that subjects became refractory to the effects of ruxolitinib treatment.

2.2.3 Drug product

Formulation: Ruxolitinib tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths have been developed as uncoated immediate release dosage forms for oral administration. The higher strength tablets are quantitatively proportional to the 5 mg tablets as all tablet strengths are compressed from a common blend. These drug products are commercially available.

2.2.4 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.

2.2.5 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). Advers 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.

2.2.5.1 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. At Week 24, there was marked improvement in the symptom scores for night sweats and itching, and the improvement occurred at all doses. Improvements in abdominal pain were smaller, and also not dose-dependent. Overall, at Week 24, patients had a median percent reduction from baseline in total symptom score (comprised of scores for abdominal discomfort/pain, itching, night sweats and bone/muscle pain) of 55%. This level of 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).

2.2.5.2 Improvement in symptoms and QoL

Symptoms of MF were assessed using a symptom diary (modified MFSAF v2.0 diary, electronic device). MF symptoms assessed included night sweats, itching, abdominal discomfort, pain under ribs on left, feeling of fullness (early satiety), muscle/bone pain and inactivity. The modified MFSAF v2.0 diary was completed by patients each night beginning at Day -7 (first day of baseline) through the Week 24 visit (25 weeks total). The proportion of patients who achieved a ≥50% improvement from baseline in the Week 24 total symptom score (which does not include inactivity) was a key secondary endpoint. A statistically significantly larger proportion of patients in the ruxolitinib arm achieved a ≥50% improvement from baseline in Week 24 total symptom score compared to the placebo arm (45.9% and 5.3%, respectively, $p<0.0001$ from Chi-square test). Remarkably, the improvement in symptoms and QoL correlated with a reduction in inflammatory cytokine levels (Verstovsek et al., 2010; Mesa et al., 2011; Verstovsek et al., 2012).

2.2.6 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 in Phase III patients.

	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)

	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 (%)**
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 hypercholesterolaemia 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. Recently reported infectious complicatios include: 1.) Progressive multifocal leukoencephalopathy (PML) in a patient with myelofibrosis. 2.) 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.

2.2.7 Warnings and precautions

Decrease in blood cell count

Treatment with ruxolitinib can cause hematologic adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with ruxolitinib. Complete blood counts should be monitored every 2-4 weeks until counts are stabilized, and then as clinically indicated and dose adjusted. It has been observed that patients with low platelet counts (<200 x 109/L) at the start of therapy are more likely to develop thrombocytopenia during treatment. Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding ruxolitinib. However, platelet transfusions may be required as clinically indicated.

Patients developing anemia may require blood transfusions.
Neutropenia (ANC<0.5 x 10^9/L) was generally reversible and was managed by temporarily withholding ruxolitinib.

Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal or viral infections. Ruxolitinib therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving ruxolitinib for signs and symptoms of infections and initiate appropriate treatment promptly.

Herpes Zoster

Physicians should educate patients about early signs and symptoms of herpes zoster infection, advising that treatment should be sought as early as possible.

Withdrawal effects

Following interruption or discontinuation of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness.

2.2.8 Contraindications

Hypersensitivity to the active substance or any of the excipients.

2.2.9 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.

2.2.10 Dosage and administration in MF

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.

2.2.11 Special populations

Renal impairment

In patients with severe renal impairment (Clcr ≤30 mL/min) the recommended starting dose based on platelet count should be reduced by approximately 50% (or as specified in country specific product labels). Patients diagnosed with severe renal impairment while receiving ruxolitinib should be carefully monitored and may need to have their doses reduced to avoid ADRs. There are limited data to determine the best dosing options for patients with end-stage renal disease on hemodialysis. Available data in this population suggest that patients on hemodialysis should be started on an initial single-dose based on platelet counts with subsequent single-doses only after each hemodialysis session, and with careful monitoring of safety and efficacy.

Hepatic impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% (or as specified in country specific product labels). Patients diagnosed with hepatic impairment while receiving ruxolitinib should be carefully monitored and may need to have their dose reduced to avoid ADRs.

2.2.12 Dose adjustment with concomitant strong CYP3A4 inhibitors

When ruxolitinib is administered with strong CYP3A4 inhibitors (such as, but not limited to, boceprevir, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) as well as fluconazole (a dual inhibitor of CYP3A4 and CYP2C9), the dose should be reduced to 10 mg twice daily (i.e., approximately 50% of the dose rounding to the nearest dosage strength). More frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib related adverse reactions is recommended upon initiation of a strong CYP3A4 inhibitor. No dose adjustment is necessary when a mild or moderate CYP3A4 inhibitor is used concomitantly with ruxolitinib. No dose adjustment is necessary when a CYP3A4 inducer (such as, but not limited to, avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifampicin, St.John's) is used concomitantly with ruxolitinib. Patients should be closely monitored and the ruxolitinib dose titrated based on safety and efficacy.

2.2.13 Women of child-bearing potential

Women of child-bearing potential must take appropriate precautions to avoid pregnancy during treatment. In case pregnancy occurs, risk-benefit evaluations must be carried out on an individual basis with careful counseling regarding potential risk to the fetus using the most recent data available. Embryo-fetal development studies with ruxolitinib in rats and rabbits did not indicate teratogenicity. Ruxolitinib was embryotoxic and fetotoxic in rats (increases in postimplantation loss and reduced fetal weights). The potential risk for humans is unknown.

2.2.14 Breast-feeding

Women taking ruxolitinib should not breast-feed.

2.2.15 Overdosage

There is no known antidote for overdoses with ruxolitinib. 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.

2.2.16 Post-marketing experience

Ruxolitinib has been granted Marketing Authorization Approval in the USA (approved in November 2011) for 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).

2.3 Protocol update

We almost completed accrual of chronic lymphocytic leukemia (CLL) patients onto protocol. We found that Ruxolitinib was well tolerated and clinically effective. None of the enrolled patients had to be removed from protocol because of adverse effect, and the vast majority of patients experienced a reduction in fatigue, as measured by the Brief Fatigue Inventory (BFI), and in other symptoms as assessed by the MD Anderson Symptom Inventory (MDSI). While a majority of patients experienced an increase in peripheral blood lymphocytes, likely because of a mobilization effect, and then a reduction in lymphocyte counts below baseline levels, we are not sure whether this effect represents a true reduction in disease burden, as outlined in the second part of the secondary objective of our protocol. Therefore we intend to increase the cohort of studied patients from 40 to 60.

3.0 PATIENT SELECTION

3.1 Eligibility

Patients with previously untreated or previously treated CLL, that do not require therapeutic intervention according to the IWCLL guidelines (Table 3) and are significantly symptomatic according to that attached symptom scale, will be eligible to enroll onto the study.

Table 3. IWCLL recommendations for the treatment of CLL (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; and RQ, research question.

A symptom scale of patients will CLL is enclosed in Appendix D. Because fatigue is a predominant symptom in patients with CLL, the primary outcome for the trial will be reduction of fatigue from baseline (ie enrollment) to 3 months, based on the patient's rating of their "worst fatigue" in the last 24 hours, a single item on the on the Brief Fatigue Inventory (BFI) (Appendix G). Mendoza et al.,1999). There is considerable consensus that a reduction of a symptom score that represents 0.5 of the standard deviation (SD) of pre-trial levels can be considered clinically meaningful (Sloan et al., 2005). A pilot study of CLL patients at MD Anderson with a sample of 126 patients demonstrated that fatigue was the most severe score reported, and the SD for this sample on the fatigue item was 2.69.

The BFI has been shown to capture reduction of fatigue in treatment of myeloproliferative neoplasm with ruxolitinib (Mascarenthas and Hoffman, 2012; Mesa et al., 2011) and has been used to demonstrate the fatigue sparing effects of abriterone with prednisone compared with prednisone alone in metastatic castration resistant prostate cancer (Sternberg et al., 2012).

Fatigue severity is but one component of the fatigue experience. The BFI also asks the patient to rate how much their fatigue interferes with function. Both fatigue severity and interference have been noted to be important metrics of fatigue (Barsevick et al., 2010). The abritarone study demonstrated a benefit for the combined treatment in reducing interference as well as severity, and we will examine fatigue interference reduction as a secondary outcome.

Finally, other symptoms may well be reduced in addition to fatigue. Ruxolitinib administration was associated with improvement in such symptoms as pain, night sweats and reduced appetite (Verstovsek et al., 2010, Mesa et al., 2011). We will use the CLL module of the MD Anderson Symptom inventory (measuring other symptoms "at their worst") of common symptoms associated with CLL.

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 and do not meet the IWCLL criteria for treatment (Hallek et al., 2008).
4) Patients may have been previously treated or previously untreated.
5) Symptomatic patients with a BFI symptom scale of 2 points or greater according to the symptom scale provided in Appendix G.
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 75 $x10^9$/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) Subjects must have discontinued all drugs used to treat CLL no later than Day -30.
10) Subjects with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.

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 an invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin completely resected intraepithelial carcinoma of the cervix and completely resected papillary thyroid and follicular thyroid cancers. Other completely resected cancers greater than 2 years may be considered after review by the PI.
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. Refer to protocol section 2.2.12 for more details.
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 for at least the 12 weeks prior to screening.
13) Subjects who are unable to complete the symptom diary (Appendix D).
14) Subjects who will need conventional therapy during the course of the study.

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 10 mg bid and dose adjustment 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 1 and Section 2.2.7).

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 2 years. Treatment beyond 2 years may be permitted after discussion with the PI. The discussion should be documented in the subject's medical record. Treatment beyond 2 years may be permitted after discussion with the PI.

4.4 Total Number of Patients to Be Enrolled

Total enrollment for this study will be 60 patients.

5.0 DOSING DELAYS/ DOSE MODIFICATIONS

5.1 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.

5.2 Dose modification

Dose adjustments for declining hematology parameters, other adverse events or for attaining a better response will be conducted according to the schema outlined in Table 4. Hematology parameters and adverse events will be assessed at every study visit. Complete blood count (CBC) will be monitored as clinically indicated and at scheduled clinic visits.

Dose adjustments can be made at MD Anderson by treating physician. For patients on dose reduction for declining hematologic parameters, dose increase may occur when hematologic parameters have improved and are stable.

Table 4. Dose (mg) adjustment schema

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

5.3 Stopping rules

A patient will be taken off study if one of the criteria from removal of study (Section 11) is met.

6.0 AGENT FORMULATION AND PROCUREMENT

Ruxolitinib tablets of 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg strengths are uncoated, immediate release dosage forms for oral administration. Ruxolitinib 5 mg tablets will be provided as an investigational study drug.

Investigational Pharmacy will dispense Ruxolitinib to the patient during visits to MDACC.

7.0 CORRELATIVE/ SPECIAL STUDIES

Patients' plasma samples and peripheral blood cells will be obtained prior to and during treatment (at the day of symptom assessment which is completed at baseline, approximately 2 weeks, and approximately 3 months from enrollment or during their next visit to the Leukemia Clinic at MDACC), or as requested by PI.

Those samples will be stored at -20°C in the P.I.'s laboratory, using appropriate de-identifiers, and patient plasma samples will be analyzed for changes in protein analytes including markers of inflammation, tumor and nutritional status. These analyses will be carried out by Incyte Corporation (Wilmington, Delaware) or Incyte Designee. Changes in B-cell receptor signaling pathways will be assessed in Dr. Estrov's laboratory using standard technology.

8.0 PATIENT EVALUATION

Patients will be evaluated in accordance with our standard of care (a 1-2 month routine physical examination and standard CBC by the patient's physician). On every clinic visit at MDACC a routine physical examination and standard laboratory tests including CBC, creatinine and ALT will be conducted. Complete Blood Counts should be monitored every 2-4 weeks until counts are stabilized.

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 F)
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 Symptom 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.

8.1 Symptom score assessment

Patients will be presented with the informed consent. They will fill out the Brief Fatigue Inventory (BFI) (Appendix G) and the MD Anderson Symptom Inventory (MDSI) (Appendix D) and if qualified, and meeting eligibility criteria and sign the informed consent, they will enroll onto the study. The patients will fill out the BFI and MDSI forms at each visit. These time points were chosen because we have observed symptom improvement in MF patients as early as 2 weeks.

8.2 Disease response assessment

Assessment of clinical response will be conducted in accordance with our standard of care (physical examination, CBC and if clinically indicated, a bone marrow aspiration).

The IWCLL response criteria (Hallek et al., 2008) (Table 5) will be used to assess disease response. If a reduction in tumor burden is observed, a bone marrow aspiration will be obtained to further assess response. **Table 5.** Response definition after treatment for patients with CLL, 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
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
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.

8.2.1 Symptom improvement response criteria

Continuous changes in symptoms will be assessed. Frequencies of 20% reduction in symptoms or a 2 point change in the BFI worst fatigue item may be reported.

8.2.2 Disease response criteria

Clinical response will be assessed in accordance with the IWCLL guidelines (Hallek et al., 2008) as outlined in Table 5.

9.0 RESPONSE CRITERIA

9.1 Symptom improvement response criteria

Continuous changes in symptoms will be assessed. Frequencies of 20% reduction in symptoms or a 2 point change in the BFI worst fatigue item may be reported.

9.2 Disease response criteria

Clinical response will be assessed in accordance with the IWCLL guidelines (Hallek et al., 2008) as outlined in Table 5.

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 required therapeutic intervention (an increase in peripheral blood lymphocyte count is expected and will not require treatment discontinuation).
4. Lack of response.
5. Unexpected events (medical or other) that would prevent the patient from staying on study.
6. Patient'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 continuous reduction in fatigue as measured by the BFI question 3 regarding the worst

fatigue in the past 24 hours, calculated from enrollment minus the score at 3 months. A higher rating on this 0-10 point scale indicates worse fatigue. Previous studies have also used this "fatigue worst" item and sometimes group patients into mild, moderate, and severe fatigue. The primary analysis set will include patients who have taken the drug for 12 weeks with no more than 1 month off drug at any time. We hope to see at least a 2 point reduction in fatigue score **(BFI #3)** or 20% reduction in all symptom items. While the primary endpoint will be analyzed in a continuous fashion, secondary endpoints may tabulate the proportion of patients with 2 point reductions in the **BFI #3 score at 3 months versus at enrollment** or 20% improvement in symptoms measured by the MDASI. Patients who drop out will be considered as failure (no change) for the primary analysis.

We will incorporate an informal futility analysis when half of the total patients have reached three months to assess whether the average change in the BFI #**3 score** is less than zero (calculated as the score at enrollment minus the score at three months). If the average at this time is less than zero, the trial will be stopped early.

Table 6 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 3 months is less than zero, and formally tests whether the change is not equal to zero at the final analysis using a *t*-test.

Table 6. Operating characteristics

True BFI difference (baseline score minus score at 3 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

The primary analysis will be based on a paired *t*-test of the worst fatigue item from the BFI. Secondary analyses will be conducted for other symptoms and the MDASI. 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 over time in symptoms.

With a total of 60 patients enrolled, we assume at least 85% of them (51 patients) will provide evaluable data at both baseline and one year after treatment. If the mean reduction of peripheral blood lymphocyte count is 20% or more, and the standard deviation of deductions among all patients is less than 40%, then we have greater than 93% power to detect the deduction, using a two-sided paired *t*-test at a significance level 0.05.

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

$$\Pr[\text{prob(toxicity)} > 0.30 \mid \text{data}] > 0.96$$

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 7 depicts stopping criteria. Stopping conditions corresponding to this probability criterion are to terminate accrual if:

Table 7. Toxicity monitoring rule 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 8.

Table 8. 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 PROTOCOL ADMINISTRATION

12.1 Protocol amendments

Changes to the protocol will be made only when protocol amendments have been signed by the principal investigator and approved by the ethical committee of the study center.

12.2 Archival of data

All patient data will be kept in the MDACC archives in accordance with institutional policy after the study has been completed. All data will be available for inspection by representatives of the regulatory authorities.

12.3 Data confidentiality

Samples will be given a de-identifier number. Only the PI (Dr. Estrov) and his co-investigators will know the patients' data.

13.0 REPORTING REQUIREMENTS

Adverse events will be reported in accordance with the Leukemia-specific Adverse Event Recording and Reporting Guidelines (Appendix C)

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.

Only unexpected AEs will be recorded in the Case Report Form (CRF). 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.

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

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.

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