ARTICLE

Primary analysis of a phase II open-label trial of INCB039110, a selective JAK1 inhibitor, in patients with myelofibrosis

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ABSTRACT

Combined Janus kinase 1 (JAK1) and JAK2 inhibition therapy effectively reduces splenomegaly and symptom burden related to myelofibrosis but is associated with dose-dependent anemia and thrombocytopenia. In this open-label phase II study, we evaluated the efficacy and safety of three dose levels of INCB039110, a potent and selective oral JAK1 inhibitor, in patients with intermediate- or high-risk myelofibrosis and a platelet count ≥50×10^9/L. Of 10, 45, and 32 patients enrolled in the 100 mg twice-daily, 200 mg twice-daily, and 600 mg once-daily cohorts, respectively, 50.0%, 64.4%, and 68.8% completed week 24. A ≥50% reduction in total symptom score was achieved by 35.7% and 28.6% of patients in the 200 mg twice-daily cohort and 32.3% and 35.5% in the 600 mg once-daily cohort at week 12 (primary end point) and 24, respectively. By contrast, two patients (20%) in the 100 mg twice-daily cohort had ≥50% total symptom score reduction at weeks 12 and 24. For the 200 mg twice-daily and 600 mg once-daily cohorts, the median spleen volume reductions at week 12 were 14.2% and 17.4%, respectively. Furthermore, 21/39 (53.8%) patients who required red blood cell transfusions during the 12 weeks preceding treatment initiation achieved a ≥50% reduction in the number of red blood cell units transfused during study weeks 1-24. Only one patient discontinued for grade 3 thrombocytopenia. Non-hematologic adverse events were largely grade 1 or 2; the most common was fatigue. Treatment with INCB039110 resulted in clinically meaningful symptom relief, modest spleen volume reduction, and limited myelosuppression.

Introduction

Myelofibrosis is a myeloproliferative neoplasm associated with progressive bone marrow fibrosis and ineffective hematopoiesis.[1,2] Patients with myelofibrosis have a reduced life expectancy and commonly experience splenomegaly and a variety of constitutional and/or spleen-related symptoms, including early satiety, night sweats, pruritus, and abdominal discomfort.[3] Although the symptoms of myelofibrosis vary among patients, for many the overall symptom burden is substantial and often has a debilitating effect on quality of life.[4-6]

Although most patients with myelofibrosis have primary disease, some develop myelofibrosis secondary to other myeloproliferative neoplasms, including poly-

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cythemia vera and essential thrombocythemia. Patients with myelofibrosis may have multiple somatic hematopoietic stem cell mutations, and nearly all carry mutations in one of three genes that have been linked to overactivation of the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway. These mutations include *JAK2*^{V617F}, a gain-of-function mutation causing constitutive JAK2 activation, *MPL* mutations that facilitate ligand-independent thrombopoietin receptor signaling through JAK2, and mutations in *CALR*.[7,8] In addition to overactive JAK2 signaling in malignant hematopoietic stem cells,[8] the dysregulation of cytokine networks that control inflammatory processes and rely on JAK1-mediated signal transduction is an important pathogenic mechanism.[9,10] A large number of inflammatory and immune mediators, such as interleukin-6, interleukin-2, and interferon-γ, are known to signal primarily through the association of either JAK1/JAK2 or JAK1/JAK3 pairing.[9]

The only therapy currently approved for the treatment of patients with intermediate- or high-risk myelofibrosis is ruxolitinib, an equipotent JAK1 and JAK2 inhibitor that has been shown in phase III clinical trials [COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment I (COMFORT-I)[11] and COMFORT-II[12]] to be highly effective in reducing myelofibrosis-related splenomegaly and symptom burden. The relative contribution of JAK1 and JAK2 inhibition to the therapeutic benefit of ruxolitinib is unclear. Patients treated with ruxolitinib experience rapid reductions in the circulating levels of inflammatory cytokines, including tumor necrosis factor α and interleukin-6.[11,13] It is likely that inhibition of JAK-STAT signaling beyond solely inhibiting neoplastic myeloproliferation is responsible for the treatment effects of ruxolitinib and, given the importance of JAK1 in the transduction of proinflammatory signals, JAK1 inhibition may be an important basis for therapeutic effects of ruxolitinib.[9] A potential benefit of selective JAK1 inhibition without JAK2 inhibition would be the elimination of myelosuppression attributable to the inhibition of JAK2-mediated hematopoiesis. To explore this possibility, we sought to determine the therapeutic benefits of INCB039110, a potent and selective inhibitor of JAK1 with low *in vitro* affinity for JAK2 (>20-fold selectivity for JAK1 over JAK2) and other members of the JAK family (>100-fold selectivity for JAK1 over JAK3 and TYK2) (*data on file*). Here we report the results of a phase II clinical study that evaluated the efficacy and safety of INCB039110 in patients with intermediate- or high-risk myelofibrosis.

Methods

Patients and study design

This open-label phase II study (*ClinicalTrials.gov identifier NCT01633372*) included adults with intermediate- or high-risk (according to the Dynamic International Prognostic Scoring System) primary myelofibrosis, post–polycythemia vera myelofibrosis, or post–essential thrombocythemia myelofibrosis, regardless of *JAK2* mutation status, with platelet count ≥50×10^9/L, hemoglobin ≥8.0 g/dL (transfusions permitted), absolute neutrophil count ≥1×10^9/L, palpable spleen or prior splenectomy, and active myelofibrosis-related symptoms. Key exclusion criteria were impaired liver function, end-stage renal disease requiring dialysis, clinically significant concurrent infections requiring therapy, unstable cardiac function, and invasive malignancies in the preceding 2 years. Prior treatment for myelofibrosis, including JAK inhibitor therapy, was not an exclusion criterion; however, eligible patients had to discontinue all prior treatment for myelofibrosis no later than 14 days before receipt of the first dose of study drug.

The study used a Simon two-stage design to assess the efficacy and safety of different doses of INCB039110 (*Online Supplementary Figure S1*). The first 20 patients were randomized to two dose cohorts (100 or 200 mg twice daily). Based on emerging data from these cohorts, patients were assigned to an additional dose cohort (600 mg once daily), with the goal of optimizing starting doses for efficacy and safety. A dose cohort was expanded to enroll an additional seven patients if at least three of the first ten patients met the primary endpoint. Based on efficacy and safety data, a dose cohort could be expanded further, by up to 40 additional patients. The primary endpoint was the proportion of patients in each dose group with a ≥50% reduction from baseline to week 12 in total symptom score (TSS), consisting of the sum of all individual scores for six myelofibrosis-related symptoms: night sweats, pruritus, abdominal discomfort, pain under the left ribs, early satiety, and bone or muscle pain. Secondary endpoints included the proportion of patients with a ≥50% reduction in TSS from baseline to week 24, the proportions of patients with a ≥35% reduction in spleen volume from baseline to weeks 12 and 24, the percentage changes from baseline to weeks 12 and 24 in TSS and spleen volume, the proportion of patients requiring red blood cell (RBC) transfusions before study entry (i.e. ≥2 units in the 12 weeks preceding study day 1) who exhibited a ≥50% decrease in transfusion frequency over any 12-week period during the study, and safety and tolerability. Changes in the percentage of patients with RBC transfusion needs were determined *ad hoc*. Additional exploratory analyses included the determination of changes from baseline in *JAK2*^{V617F} allele burden at weeks 12 and 24 and changes from baseline in plasma cytokine levels at week 4.

The study protocol was approved by the local institutional review boards and ethics committees, and the study was conducted in accordance with the ethical principles laid out in the Declaration of Helsinki, the guidelines of the International Conference on Harmonisation for Good Clinical Practice, and all applicable federal and local regulations. All patients provided written informed consent before treatment initiation.

Assessments and analyses

Patients had scheduled study visits at screening, baseline, day 1, and weeks 4, 8, 12, 16, 20, and 24. Patients assessed the severity of disease-related symptoms daily, using the modified Myelofibrosis Symptom Assessment Form v3.0 electronic diary, in which each symptom is ranked on a scale of 0 (absent) to 10 (worst imaginable). Spleen volume was assessed by magnetic resonance imaging or computed tomography at weeks 12 and 24. Patient Global Impression of Change (PGIC) of myelofibrosis symptoms was assessed at post-baseline visits using a questionnaire with a 7-point rating scale (1: very much improved, 2: much improved, 3: minimally improved, 4: no change, 5: minimally worse, 6: much worse, 7: very much worse). Non-hematologic adverse events were reported using the Common Terminology Criteria for Adverse Events v4.03. Reporting of hematologic adverse events was based on laboratory data, except that grade 4 anemia was reported based on Common Terminology Criteria for Adverse Events v4.03.

Genomic DNA isolation from peripheral blood and *JAK2*^{V617F} assays were performed as described previously[14] on samples collected at baseline and weeks 12 and 24. The percentage change from baseline in allele burden was calculated for all patients harboring the *JAK2*^{V617F} mutation at baseline.

Cytokines were measured in plasma samples collected at baseline and week 4 using the Myriad RBM HumanMap® Panel

(Myriad RBM, Austin, TX, USA). Plasma cytokine levels were analyzed using OmicSoft's Array Studio software (OmicSoft Corporation, Cary, NC, USA). Changes at week 4 relative to baseline were determined and converted to Log_2 scale and heat maps were generated using hierarchical clustering.

For calculations of the proportion of patients achieving ≥50% reduction from baseline in TSS and those achieving ≥10% reduction from baseline in spleen volume, all patients who had baseline data were included in the analyses. Patients who discontinued treatment before the scheduled time of post-baseline response assessments (week 12 or 24) were considered to be non-responders.

All other analyses at specific time-points were based on observed cases, and patients who discontinued treatment before the time of the post-baseline assessment were excluded from analysis at those time-points. Adverse events were assessed in the safety evaluable population, which included all patients who took at least one dose of study medication.

Results

Patients

Enrollment is complete and 87 patients have been treated with INCB039110, including 10, 45, and 32 patients in the 100 mg twice-daily, 200 mg twice-daily, and 600 mg once-daily cohorts, respectively. A total of 10, 42, and 31 patients in the 100 mg twice-daily, 200 mg twice-daily, and 600 mg once-daily cohorts, respectively, were evaluable for the primary endpoint. Overall, 5/10 (50.0%) patients in the 100 mg twice-daily cohort, 16/45 (35.6%) patients in the 200 mg twice-daily cohort, and 10/32 (31.3%) patients in the 600 mg once-daily cohort discontinued treatment prior to week 24. Primary reasons for discontinuation of therapy included adverse events (7 patients), disease progression (6 patients), consent withdrawal (5 patients), death (2 patients), and other reasons (11 patients, mostly due to a perceived lack of response to therapy as judged by the physician or patient). Both deaths were considered by the investigators to be unrelated to treatment.

The mean age of the patients was 64 years and 84% had intermediate-1 (37%) or intermediate-2 (47%) risk myelofibrosis according to the Dynamic International Prognostic Scoring System. The mean spleen volume at baseline was 2442.7 cm^3 and the mean hemoglobin concentration was 10.2 g/dL. As shown in Table 1, patients' demographics and disease characteristics at baseline were similar across cohorts, except for myelofibrosis disease type and platelet counts. A *post hoc* analysis showed that only baseline platelet count varied significantly (P=0.0111 for differences between dose groups, analysis of variance); the differences in myelofibrosis disease type were not statistically significant (P=0.1745, chi-square test).

Table 1. Patients' demographic and disease characteristics at baseline by cohort.

Characteristic	100 mg twice daily (n=10)	200 mg twice daily (n=45)	600 mg once daily (n=32)
Age, mean (range), years	65.9 (56-80)	63.2 (35-84)	64.0 (35-81)
MF type, n (%)*			
Primary MF	7 (70.0)	28 (62.2)	13 (40.6)
Post–essential thrombocythemia MF	2 (20.0)	8 (17.8)	13 (40.6)
Post–polycythemia vera MF	1 (10.0)	9 (20.0)	6 (18.8)
DIPSS risk, n (%)			
Intermediate-1	4 (40.0)	18 (40.0)	10 (31.3)
Intermediate-2	4 (40.0)	19 (42.2)	18 (56.3)
High	2 (20.0)	8 (17.8)	4 (12.5)
JAK2^{V617F}-positive, n (%)	5† (55.6)	31 (68.9)	22 (68.8)
Prior JAK inhibitor therapy, n (%)	4 (40.0)	14 (31.1)	2 (6.3)
Spleen volume, mean ± SD, cm^3	2429±1074	2588±1709	2247±1456
Hemoglobin, mean ± SD, g/L	96±14	102±20	105±20
Platelet count, mean ± SD (range), × 10^9/L‡	109.3±61.2 (15-202)	211.0±192.5 (57-1084)	339.7±309.0 (58-1470)

DIPSS: Dynamic International Prognostic Scoring System; MF: myelofibrosis; SD: standard deviation. *P=0.1745 for differences between dose groups (chi-square test). †Nine patients in the 100 mg twice-daily cohort were evaluable for *JAK2*^{V617F} status. ‡P<0.05 for differences between dose groups (analysis of variance).

Symptom improvement and spleen volume reduction

The 100 mg twice-daily cohort was not expanded beyond stage 1 because only two of ten (20.0%) patients achieved the primary endpoint (≥50% reduction in TSS from baseline to week 12). In both patients, ≥50% reduction in TSS was maintained at week 24. The 200 mg twice-daily and 600 mg once-daily cohorts met the criteria for expansion; 15/42 (35.7%) and 10/31 (32.3%) patients, respectively, achieved the primary endpoint. The corresponding proportions of patients with a ≥50% reduction in TSS from baseline at week 24 were 28.6% and 35.5% (Figure 1A). Based on data evaluable at the respective time-points, patients in the 200 mg twice-daily cohort had a median reduction in TSS of 45.8% (n=34) and 48.6% (n=25) at week 12 and week 24, respectively, and the corresponding values for the 600 mg once-daily cohort were 37.2% (n=28) and 46.7% (n=23). Median reductions in TSS or spleen volume were not calculated for the 100 mg twice-daily cohort because of the high discontinuation rate in this cohort. The majority of patients with evaluable data at weeks 12 and/or 24 had some degree of symptom improvement (Figure 1B). Two patients experienced percentage increases in TSS outside the range shown due to very low TSS values at baseline; one patient had an increase from 0.29 at baseline to 1.86 at week 12 (representing a 550% increase), and the other had an increase from 2.29 at baseline to 7.14 at week 24 (representing a 212.5% increase). Based on the results of the PGIC questionnaire, many patients experienced substantial symptom improvement within the first 4 weeks of therapy, with 50.0% and 46.9% of evaluable patients in the 200 mg twice-daily and 600 mg once-daily cohorts, respectively, reporting that their myelofibrosis-related symptoms were much or very much improved. Among patients who remained on therapy, improvements on the PGIC were generally maintained throughout the 24-week duration of the study (*Online Supplementary Figure S2*).

For the 200 mg twice-daily and 600 mg once-daily cohorts, median spleen volume reductions for patients with evaluable data were 14.2% (n=37) and 14.5% (n=31), respectively, at week 12 and 17.4% (n=31) and 17.1% (n=24) at week 24. The proportions of patients in the 200 mg twice-daily and 600 mg once-daily cohorts who had a ≥10% reduction in spleen volume at week 12 were 52.3% and 59.4%, respectively; the corresponding proportions at week 24 were 52.3% and 46.9% (Figure 2A). Across all three cohorts, a ≥35% spleen volume reduction was

achieved by five patients at week 12 and ten patients at week 24 (Figure 2B).

Safety and tolerability

The median (range) exposure to INCB039110 was 102 (23-519) days in the 100 mg twice-daily cohort, 268 (22-535) days in the 200 mg twice-daily cohort, and 197 (58-343) days in the 600 mg once-daily cohort. The most common non-hematologic adverse events regardless of causality are shown in Table 2; most were grade 1 or 2. Grade ≥3 non-hematologic adverse events that occurred in more than one patient were: pneumonia, dyspnea, and hypertension (3 patients each), and congestive heart failure, rectal hemorrhage, asthenia, pyrexia, urinary tract infection, hyperkalemia, increased alkaline phosphatase, and acute renal failure (2 patients each). These 25 events occurred in 18 unique patients. Although infections were common (44.8%), including upper respiratory tract infections in 19.5% of patients (*Online Supplementary Table S1*), most were mild or moderate, and only four cases (1 each of bronchitis, folliculitis, Herpes simplex, and urinary tract infection) were considered treatment-related by the investigator. All of these four cases were grade 2 and not considered serious, and all resolved without changes to study treatment. Two patients (both in the 600 mg once-daily cohort) died during the study: a 62-year old patient died of pneumonia after approximately 5 months on therapy, and a 61-year old patient died of unspecified causes potentially related to disease progression after slightly less than 4 months on therapy. Both deaths were considered by the investigator to be unrelated to treatment.

New or worsening grade 3 or 4 hematologic adverse events by dose group are shown in Table 3. Overall, 32.5% of patients experienced grade 3 anemia, the majority of whom had grade 2 anemia at baseline (*Online Supplementary Table S2*), and none experienced grade 4 anemia. New or worsening grade 3 or 4 thrombocytopenia occurred in 24.4% and 4.7% of patients, respectively; many of these patients had grade 2 thrombocytopenia at baseline (*Online Supplementary Table S3*). One patient discontinued therapy because of grade 3 thrombocytopenia. Twenty-six patients had bleeding events, including two (20.0%), 15 (33.3%), and nine (28.1%) patients in the 100 mg twice-daily, 200 mg twice-daily, and 600 once-daily cohorts, respectively. Of those, six patients had grade 3 bleeding events: rectal hemorrhage (n=2) and upper gastrointestinal hemorrhage, epistaxis, hematoma, and hematochezia (n=1 each). Hematochezia occurred when the patient had a platelet count of $<50\times10^9$/L; the other bleeding events did not occur in the presence of grade ≥3 thrombocytopenia. There were no grade 4 bleeding events.

In general, hemoglobin levels were stable over the course of treatment, regardless of transfusion status at baseline and during the study (Figure 3A-C). Of 48

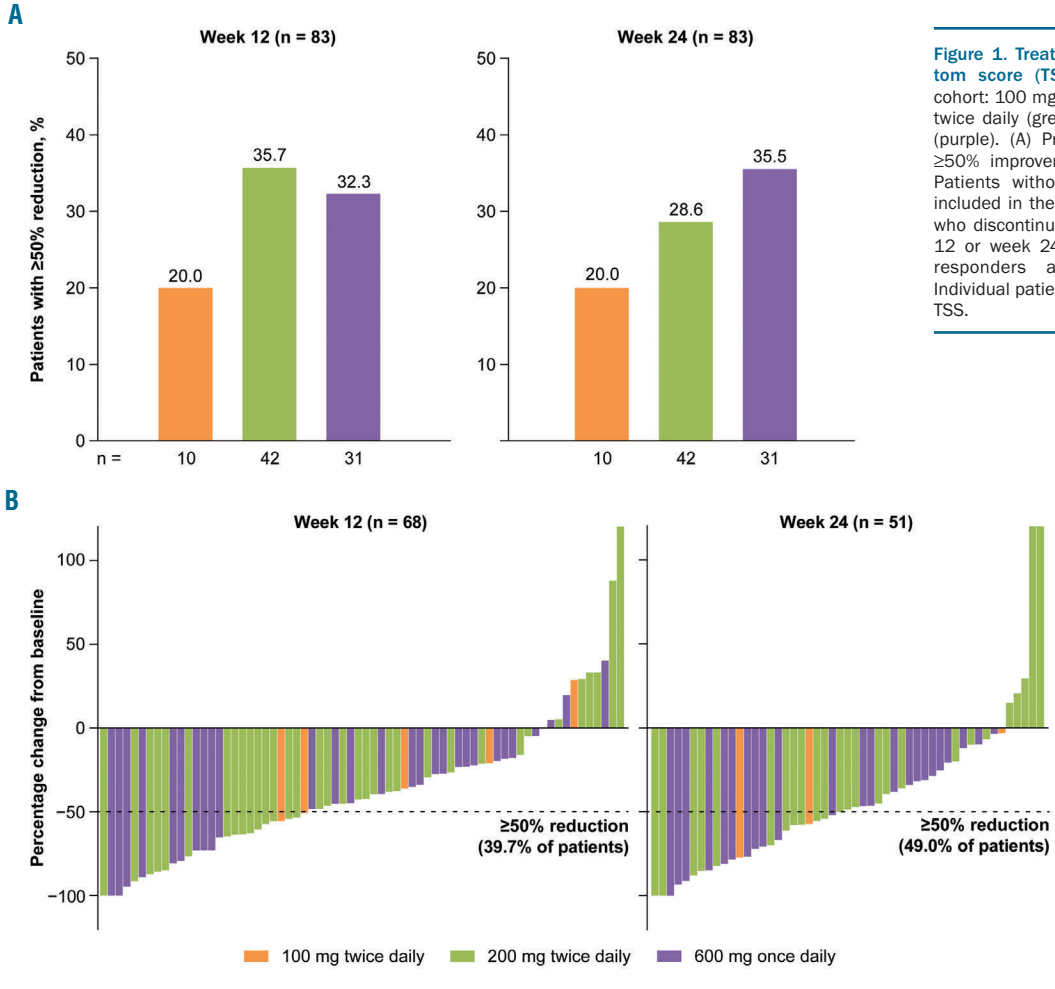

Figure 1. Treatment effects on total symptom score (TSS). Results are shown by cohort: 100 mg twice daily (orange), 200 mg twice daily (green), and 600 mg once daily (purple). (A) Proportion of patients with a ≥50% improvement in TSS from baseline. Patients without baseline data were not included in the responder analysis; patients who discontinued therapy prior to the week 12 or week 24 visit were considered non-responders at those time-points. (B) Individual patients' changes from baseline in TSS.

patients who did not require RBC transfusions during the 12 weeks preceding treatment initiation, only three patients required ≥2 units of RBC transfusions during both weeks 1-12 and weeks 13-24. A total of 39 patients required RBC transfusions during the 12 weeks preceding treatment initiation, receiving a median of 4 RBC units. Of those, six (15.4%) patients did not require RBC transfusions during the treatment period. Furthermore, 21/39 (53.8%) patients achieved a ≥50% reduction in RBC units transfused during the study, including 1/3 (33.3%) in the 100 mg twice-daily cohort with a reduction of eight RBC units, 15/24 (62.5%) in the 200 mg twice-daily cohort with a median reduction of three units (range, 2 to 10 units) and 5/12 (41.7%) in the 600 mg once-daily cohort with a median reduction of seven units (range, 2 to 28 units).

Mean platelet counts decreased slightly over time in the 100 mg twice-daily cohort and remained stable in the 200 mg twice-daily cohort. In the 600 mg once-daily cohort, mean platelet counts gradually decreased during the 24-week study period but remained within normal limits (Figure 3D).

JAK2^{V617F} allele burden and cytokine profile

Overall, 68% (58/85) of evaluable patients were *JAK2*^{V617F}-positive at baseline; the mean *JAK2*^{V617F} allele burden was 65.6% among these patients (Table 1). Mean percentage changes from baseline (standard deviation) in *JAK2*^{V617F} allele burden were –4% (14%) at week 12 and –4% (18%) at week 24, with no significant difference in allele burden changes between the 200-mg and 600-mg cohorts at either time-point. Analysis of the expression levels of a large number of plasma markers revealed global changes from baseline to week 4 in cytokine expression patterns in all patients. The plasma levels of a number of key inflammatory markers, such as C-reactive protein, interleukin-6, interleukin-10, CD40 ligand, RANTES, and vascular endothelial growth factor, decreased in most patients following 4 weeks of treatment (Figure 4).

Discussion

In this study, patients with myelofibrosis treated with the selective JAK1 inhibitor INCB039110 at doses of 200 mg twice daily or 600 mg once daily experienced clinically meaningful improvements in myelofibrosis-related symptoms at weeks 12 and 24. Although the 100 mg twice-daily cohort was not selected for expansion, two patients experienced a ≥50% reduction in myelofibrosis-related symptoms at week 12, which was maintained at week 24.

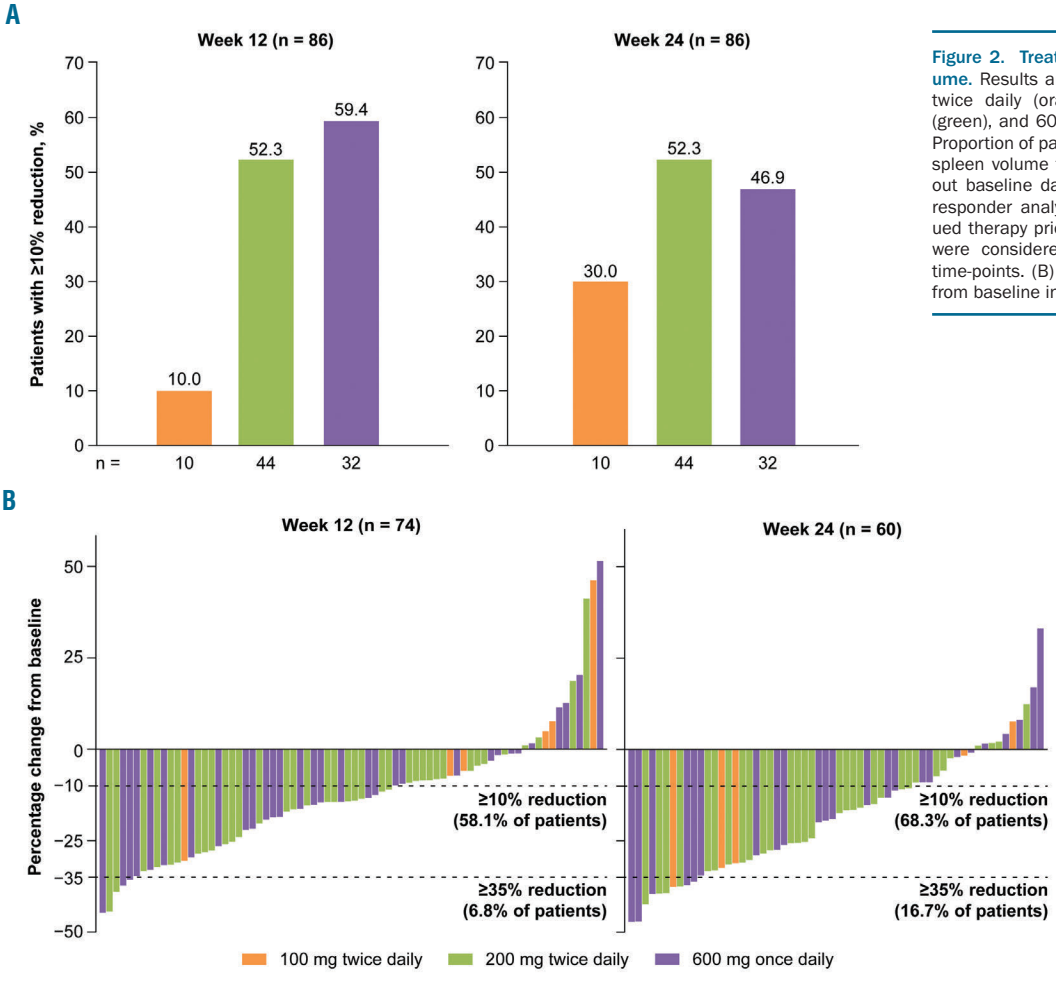

Figure 2. Treatment effects on spleen volume. Results are shown by cohort: 100 mg twice daily (orange), 200 mg twice daily (green), and 600 mg once daily (purple). (A) Proportion of patients with ≥10% reduction in spleen volume from baseline. Patients without baseline data were not included in the responder analysis; patients who discontinued therapy prior to the week 12 or 24 visit were considered non-responders at those time-points. (B) Individual patients' changes from baseline in spleen volume.

INCB039110 treatment resulted in modest spleen size reduction, an expected result given the lack of JAK2 inhibition. Notably, INCB039110 overall was less effective in providing spleen size reductions than ruxolitinib and some JAK2 inhibitors tested in phase III clinical trials.[11,12,15,16] Few patients in our study experienced ≥35% spleen volume reduction; however, among patients who remained on treatment, the proportion achieving ≥35% spleen volume reduction increased from week 12 to 24. Additionally, more than half of the patients treated with 200 mg twice daily and nearly half of those treated with 600 mg once daily experienced a ≥10% spleen volume reduction at week 24, which was associated with clinically meaningful symptom improvement in patients treated with ruxolitinib in COMFORT-I.[17] Consistent with its mechanism of action, INCB039110 had only minimal effects on *JAK2*^{V617F} allele burden during the 24-week study period.

Our findings reinforce the theory that JAK1 inhibition is an important mechanism of symptom control in patients with myelofibrosis. In our study, 28.6% and 35.5% of patients in the 200 mg twice-daily and 600 mg once-daily cohorts, respectively, achieved ≥50% reduction in TSS at week 24. Although studies cannot be directly compared given differences in study design, symptom assessment methods, and patient populations, overall, these percentages are similar to corresponding values reported for fedratinib, a selective JAK2 inhibitor, and pacritinib, a JAK2/FLT3 inhibitor, in large randomized phase III studies. In JAKARTA, a placebo-controlled phase III study of fedratinib in patients with intermediate-2 or high-risk myelofibrosis, the proportion of patients treated with fedratinib who achieved ≥50% reduction in TSS (assessed with the modified Myelofibrosis Symptom Assessment Form) at week 24 was 34% or 36% depending on dose (7% for placebo).[15] In PERSIST-1, a phase III study of pacritinib *versus* best available therapy (excluding ruxolitinib) in patients with intermediate- or high-risk myelofibrosis, 24.5% of patients in the pacritinib arm (6.5% for best available therapy) achieved a ≥50% reduction in TSS (assessed with the Myeloproliferative Neoplasm Symptom Assessment Form) at week 24.[16] The proportions of patients with this degree of symptom response in JAKARTA, PERSIST-1, and the current study were smaller than the corresponding proportion seen with ruxolitinib in the COMFORT-I study (45.9% *versus* 5.3% with placebo).[11] The degree of symptom response was also high in a phase I/II trial of the JAK1/JAK2 inhibitor momelotinib, in which 60% to 100% of patients experienced ≥50% reductions in some individual symptoms at 3 and 6 months; however, TSS was not assessed.[18] Overall, these data support the notion that JAK1 and JAK2 inhibition contribute to improvement in myelofibrosis-related symptoms; however, dual inhibition of JAK1 and JAK2 may provide more effective symptom mitigation than is achievable with inhibition of either JAK isoform alone. Consistent with its effect on symptoms, INCB039110 treatment rapidly led to global reductions in plasma inflammatory makers. Notably, expression levels of C-reactive protein, a biomarker of acute inflammation, were markedly reduced in most patients. These changes in inflammatory markers are consistent with those seen in ruxolitinib-treated patients with myelofibrosis[11,13] and support the notion that JAK1 inhibition can play a vital role in reducing disease-related inflammation in patients with myelofibrosis.

INCB039110 was generally well tolerated, and non-hematologic adverse events were generally grade 1 or 2. Only four patients had infections that were considered treatment related, but of those none was serious or affected study treatment. Immunosuppression, primarily affecting T-cell function, has been offered as an explanation for the occurrence of treatment-related infections in the case of ruxolitinib,[19] and it is likely that ruxolitinib-mediated immunosuppression is at least in part attributable to JAK1 inhibition. The potential immunosuppressive effects of INCB039110 have not been investigated.

Our findings suggest that selective JAK1 inhibition is not associated with high degrees of myelosuppression. Mean platelet counts at baseline varied among dose groups. In the group of patients who received 100 mg twice daily, the mean platelet count decreased slightly from a low baseline value (109.3×10^9/L) over the course of the study, whereas it remained relatively stable in the cohort that received 200 mg twice daily. The mean platelet count in the 600 mg once-daily cohort decreased over time from a high baseline value (339.7×10^9/L) and remained within the normal range over the 24-week period of the study. Given that the study included patients with low platelet counts at base-

Table 2. Non-hematologic adverse events of any grade (regardless of causality).*

Patients, n (%)	100 mg twice daily (n=10)	200 mg twice daily (n=45)	600 mg once daily (n=32)
Fatigue	3 (30.0)	18 (40.0)	4 (12.5)
Nausea	3 (30.0)	9 (20.0)	6 (18.8)
Upper respiratory tract infection	3 (30.0)	8 (17.8)	6 (18.8)
Constipation	1 (10.0)	10 (22.2)	4 (12.5)
Cough	1 (10.0)	10 (22.2)	4 (12.5)
Diarrhea	2 (20.0)	8 (17.8)	5 (15.6)
Dyspnea	1 (10.0)	6 (13.3)	6 (18.8)
Peripheral edema	1 (10.0)	9 (20.0)	3 (9.4)
Pyrexia	1 (10.0)	6 (13.3)	5 (15.6)
Pain in extremity	2 (20.0)	7 (15.6)	2 (6.3)
Abdominal pain	2 (20.0)	5 (11.1)	2 (6.3)
Night sweats	1 (10.0)	5 (11.1)	3 (9.4)
Vomiting	0	8 (17.8)	1 (3.1)
Dizziness	0	6 (13.3)	3 (9.4)

*In >10% of all patients.

Table 3. Summary of grade ≥3 hematologic adverse events.*

Patients, n (%)	100 mg twice daily	200 mg twice daily	600 mg once daily
Anemia	n=9	n=42	n=32
Grade 3	3 (33.3)	16 (38.1)	8 (25.0)
Grade 4*	0	0	0
Thrombocytopenia	n=9	n=45	n=32
Grade 3	4 (44.4)	13 (28.9)	4 (12.5)
Grade 4	0	3 (6.7)	1 (3.1)
Neutropenia	n=10	n=43	n=32
Grade 3	1 (10.0)	2 (4.7)	0
Grade 4	0	1 (2.4)	0

*Events were graded based on laboratory data, except for the reporting of grade 4 anemia, which was based on Common Terminology Criteria for Adverse Events v4.03 classification.

line (≥50×10⁹/L to <100×109/L), it is noteworthy that only one patient discontinued treatment because of thrombocytopenia (grade 3). Mean hemoglobin levels remained relatively stable from baseline to week 24 in the group of 48 patients who did not require transfusions prior to study entry, and only 6% of these patients required two or more units of RBC transfusions during both weeks 1-12 and weeks 13-24 of the study. Importantly, slightly more than half of the patients who required RBC transfusions before beginning INCB039110 treatment experienced clinically meaningful reductions in RBC transfusions while on therapy.

In COMFORT-I, patients treated with the JAK1/JAK2 inhibitor ruxolitinib had temporary decreases in hemoglobin values during the first 8 to 12 weeks of therapy, and a decrease in platelet count was identified as a dose-limiting adverse effect of ruxolitinib therapy.[11,20] The proportions of patients who experienced grade ≥3 anemia and grade ≥3 thrombocytopenia with ruxolitinib were 45.2% and 12.9%, respectively (placebo, 19.2% and 1.3%, respectively); however, very few patients discontinued therapy because of cytopenias.[11] Furthermore, results of the similarly designed phase III JAKARTA study showed high rates of grade ≥3 anemia (fedratinib, 43% and 60%, depending on dose, *versus* 25% for placebo) and grade ≥3 thrombocytopenia (fedratinib, 17% and 27% *versus* 9% for placebo).[15] These findings from randomized placebo-controlled studies are consistent with myelosuppression as an expected consequence of JAK2 inhibition, as JAK2 signaling is required for normal thrombopoiesis and erythropoiesis. However, according to data from PERSIST-1, presented at the 2015 annual meeting of the American Society of Clinical Oncology, 14.5% and 2.3% of patients in the pacritinib arm had grade 3 or 4 anemia, respectively (*versus* best available therapy, 12.3% and 2.8%, respectively), and 5.5% and 6.4% had grade 3 or 4 thrombocytopenia, respectively (*versus* best available therapy, 6.6% and 2.8%, respectively). Although the assessment of hematologic adverse events in PERSIST-1 was based on investigator reports and not on laboratory analyses as in the ruxolitinib and fedratinib studies, these data suggest that the hematolog-

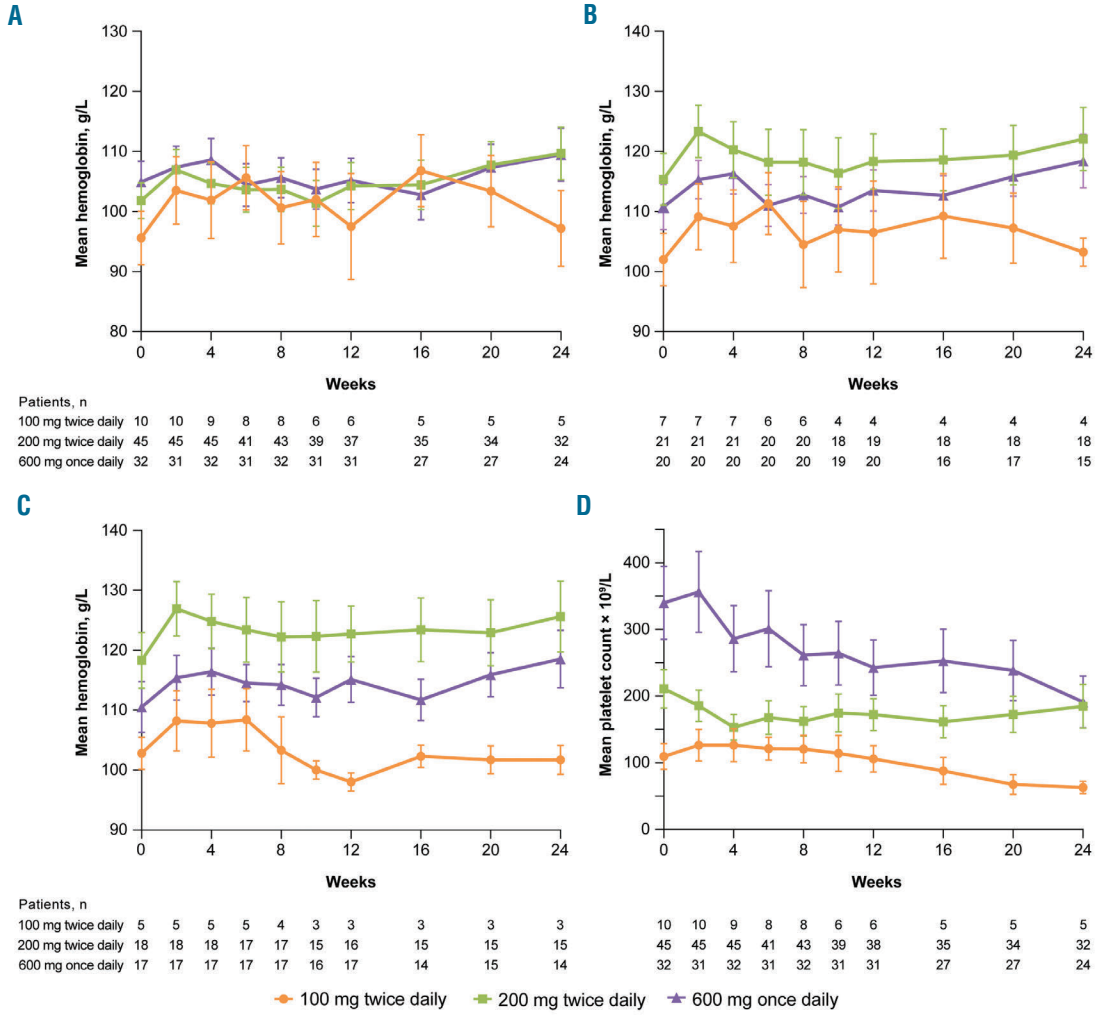

Figure 3. Mean hemoglobin level and platelet count over time by dose cohort. Mean hemoglobin for (A) all patients, (B) patients who did not require transfusion before study entry, and (C) patients who did not require transfusion before study entry or during the study. (D) Mean platelet count over time.

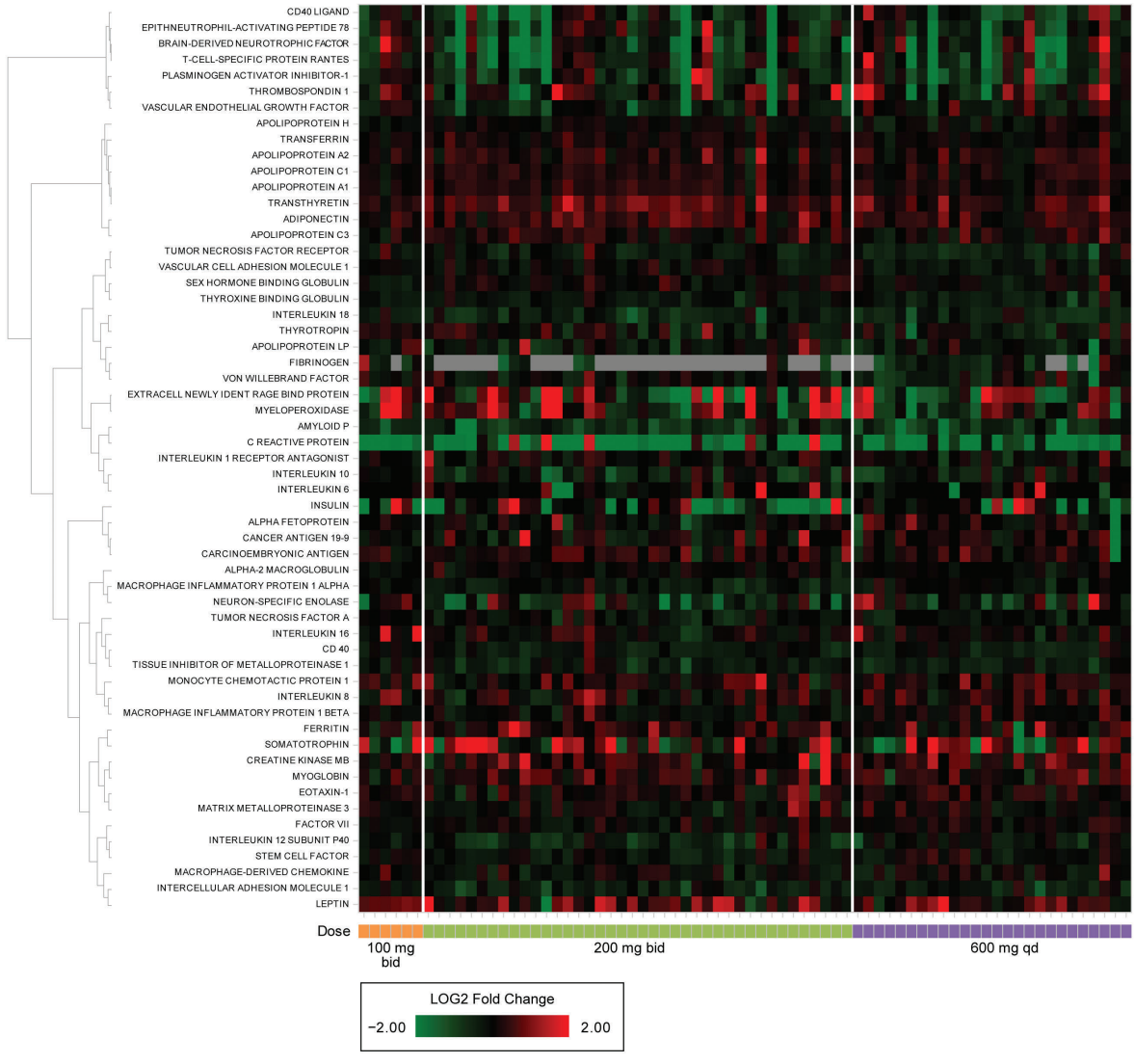

Figure 4. Changes from baseline in plasma cytokine levels at week 4. Individual patients are presented in each column, and each row is a plasma marker. Green denotes decreased levels at week 4 *versus* baseline and red denotes increased levels at week 4 *versus* baseline, with the color intensity representing the magnitude of the change on a $\log_2$ scale. Gray denotes missing data points that were not available for analysis. bid: twice daily; qd, once daily.

ic toxicity of JAK2 inhibitors may vary substantially, likely due to off-target effects that may offset myelosuppression mediated by JAK2 inhibition. In this context it is worth noting that the JAK1 and JAK2 inhibitor momelotinib has been reported to provide anemia responses.[18] Based on preliminary evidence, this benefit may be attributable to the off-target inhibition of activin receptor-like kinase-2 and the consequent reduction of hepcidin production leading to enhanced erythropoiesis.[21] In the current study, 32.5% of patients experienced grade 3 anemia (defined by laboratory values) while on study, the majority of whom had grade 2 anemia at baseline, and no patients experienced grade 4 anemia. Grade 3 or 4 thrombocytopenia (defined by laboratory values) occurred in 29.1% of patients, most commonly in the 100 mg twice-daily cohort, which had a median platelet count at baseline of 105.5×10^9/L.

In light of its limited hematologic toxicity and its efficacy in myelofibrosis symptom relief, INCB039110 may be useful in the future as part of combination therapy with agents that have complementary activity or dose-limiting hematologic toxicities, such as Hedgehog pathway inhibitors (e.g., sonidegib), phosphatidylinositol 3-kinase inhibitors, histone deacetylase inhibitors (e.g., panobinostat), and hypomethylating agents (e.g., 5-azacytidine).[22,23] Combinations involving selective JAK1 inhibition instead of JAK1/JAK2 inhibition may offer the potential for similar efficacy with less myelosuppression, although this has not been confirmed in clinical trials.

Although a long-term, placebo-controlled trial or comparative studies with other JAK inhibitors would provide a more complete clinical picture and a deeper understanding of the relative contributions of JAK1 and JAK2 inhibition in myelofibrosis, the findings of this phase II study provide preliminary evidence that selective JAK1 inhibition with INCB039110 can provide effective relief of myelofibrosis-related symptoms with limited hematologic toxicity. Furthermore, the results of this study contribute to a better understanding of JAK1 inhibition as a therapeutic target.

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