Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 3120973 A1 2020/06/04

(21) 3 120 973

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2018/11/27
(87) Date publication PCT/PCT Publication Date: 2020/06/04
(85) Entrée phase nationale/National Entry: 2021/05/25
(86) N° demande PCT/PCT Application No.: US 2018/062534
(87) N° publication PCT/PCT Publication No.: 2020/112086

(51) Cl.Int./Int.Cl. *A61K 31/55* (2006.01), *A61K 31/519* (2006.01), *A61P 35/00* (2006.01), *A61P 35/02* (2006.01), *A61P 7/06* (2006.01)

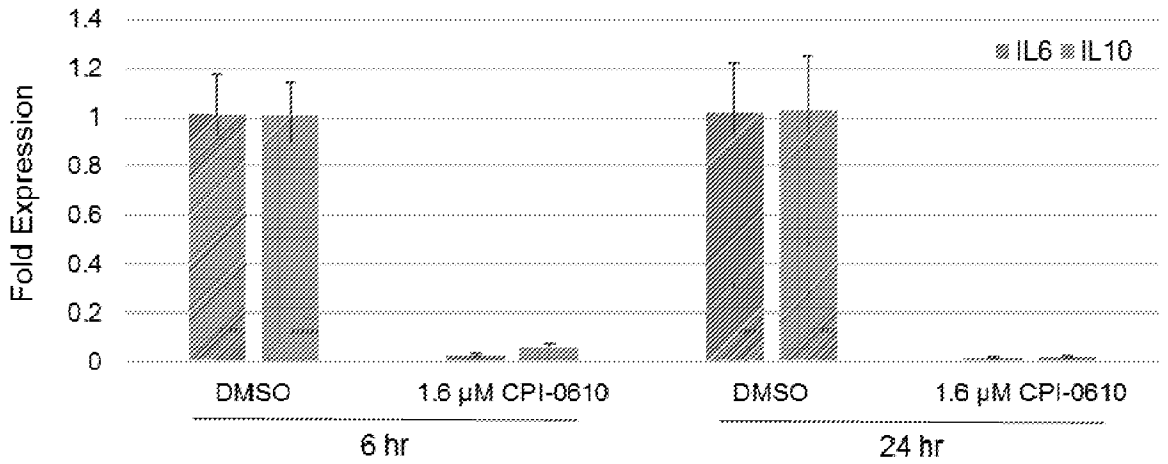
(71) Demandeur/Applicant:
CONSTELLATION PHARMACEUTICALS, INC., US

(72) Inventeurs/Inventors:
SENDEROWICZ, ADRIAN, US;
COOPER, MICHAEL, US

(74) Agent: MARKS & CLERK

(54) Titre : METHODES DE TRAITEMENT DE TROUBLES MYELOPROLIFERATIFS
(54) Title: METHODS OF TREATING MYELOPROLIFERATIVE DISORDERS

FIG. 1



(57) Abrégé/Abstract:
The present disclosure relates to the use of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, and pharmaceutically acceptable salts thereof, for treating myelofibrosis.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 June 2020 (04.06.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/112086 A1

(51) International Patent Classification:
A61K 31/55 (2006.01) *A61P 35/00* (2006.01)
A61K 31/519 (2006.01) *A61P 35/02* (2006.01)
A61P 7/06 (2006.01)

(21) International Application Number:
PCT/US2018/062534

(22) International Filing Date:
27 November 2018 (27.11.2018)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant: **CONSTELLATION PHARMACEUTICALS, INC.** [US/US]; 215 First Street, Suite 200, Cambridge, MA 02142 (US).

(72) Inventors: **SENDEROWICZ, Adrian**; 7 Park Avenue, Unit 1, Somerville, MA 02144 (US). **COOPER, Michael**; 88 Sidney Street, Cambridge, MA 02139 (US).

(74) Agent: **DAVIS, Steven, G.** et al.; McCarter & English, LLP, 265 Franklin Street, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

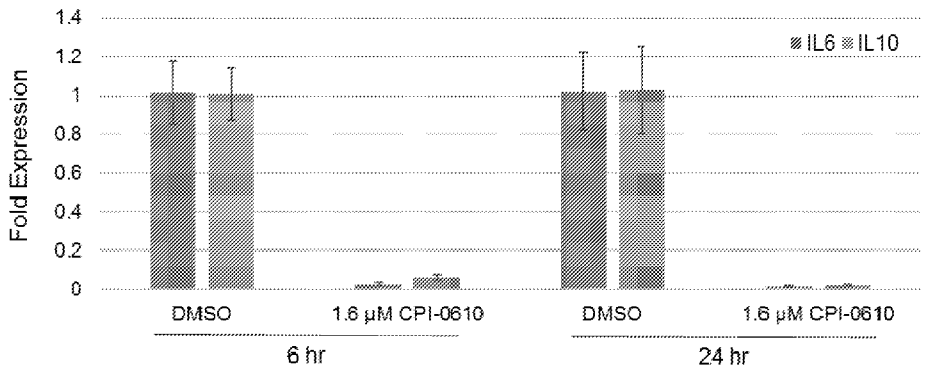
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*

WO 2020/112086 A1

(54) **Title:** METHODS OF TREATING MYELOPROLIFERATIVE DISORDERS

FIG. 1



(57) **Abstract:** The present disclosure relates to the use of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, and pharmaceutically acceptable salts thereof, for treating myelofibrosis.

METHODS OF TREATING MYELOPROLIFERATIVE DISORDERS

BACKGROUND

[0001] Myeloproliferative disorders are diseases of the bone marrow and blood. Myelofibrosis, for example, is a clonal myeloproliferative disease that is characterized by exaggerated abnormalities in megakaryocytes. The abnormal megakaryocytes are attributed primarily to dysregulation of the JAK/STAT pathway, although there is dysregulation in a number of other pathways as well. Due to the multiple pathways affected and the array of downstream effects, myelofibrosis is a complex, heterogeneous disease with many inter-related features. The abnormal megakaryocytes release excess platelets and cytokines, both pro-inflammatory and pro-fibrotic (transforming growth factor beta [TGF-ß]), into the bone marrow. The pro-inflammatory cytokines lead to debilitating constitutional symptoms and exacerbate the deposition of collagen signaled by pro-fibrotic pathways. Bone marrow fibrosis is the hallmark of myelofibrosis, although diagnosis is not necessarily dependent on it. The bone marrow fibrosis is the key feature that causes the morbidity and mortality associated with the disease. The bone marrow fibrosis and inflammatory state of myelofibrosis often lead to cytopenias, extramedullary hematopoiesis (EMH), organomegaly such as splenomegaly and hepatomegaly and a myriad of constitutional symptoms.

[0002] Myelofibrosis is a serious disease in that it is both life-threatening and greatly diminishes the quality of life of the patient before it affects survival. The two most common causes of death are conversion to acute myeloid leukemia (AML) and progression of the disease. The treatment paradigm is dictated by the number of risk factors present, which then correlate with different survival rates. While allogeneic hematopoietic stem cell transplantation (HCT) can be curative, it is associated with its own morbidity and mortality, which limit its use to those eligible patients whose prognosis is worse (< 5 years) than the risk of moving forward with the transplant. The remaining treatments are more palliative in nature, either due to their mechanism of action (e.g., treatments specifically focused on the anemia that is frequently associated with myelofibrosis) or due to the restricted effects that the treatment can elicit (e.g., the standard of care ruxolitinib).

[0003] Ruxolitinib, a JAK1/2 inhibitor, is the only approved therapy indicated for the treatment of myelofibrosis. JAK is a key regulator in hematopoiesis, immune regulation, growth and embryogenesis (Stahl M, Zeidan AM (2017). Management of Myelofibrosis: JAK Inhibition and Beyond. Expert Rev Hematol; 17(5): 459-477). Dysregulated JAK signaling can lead to increased thrombopoietin signaling, which is believed to be one of the

causes of increased megakaryocyte production and platelets in myelofibrosis. Further, JAK signaling is implicated in the release of pro-inflammatory cytokines and growth factors that cause constitutional symptoms and splenomegaly: JAK-1 plays a role in the signaling of pro-inflammatory cytokines (e.g., IL-1, IL-6, TNF-α), the cause of systemic symptoms in myelofibrosis and JAK-2 impacts growth factors and other cytokines (e.g., IL-3, IL-5) that are believed to promote splenomegaly in myelofibrosis. Through this mechanism of action, ruxolitinib has demonstrated an ability to reduce the spleen volumes and symptoms of myelofibrosis patients, thereby improving their quality of life. Unfortunately, however, there are a number of limitations with the current use of ruxolitinib.

[0004] Ruxolitinib is considered a palliative treatment due to its lack of disease-modifying effects. It does not affect the mutant allele burden or bone marrow fibrosis (Novel Therapies for Myelofibrosis, 2017, Curr Hematol Malig Rep; 12(6): 611-624). In addition, constitutional symptoms will revert back after a week off of ruxolitinib treatment (see Tefferi A (2017); Management of Primary Myelofibrosis; UpToDate; 1-23). Next, anemia negatively impacts patient quality of life, has the highest power of predicting shortened survival, and limits access to optimal standard of care. Ruxolitinib is not a viable treatment option for some anemic patients because ruxolitinib is known to decrease red blood cell production and hemoglobin levels. Anemic patients, for example, are either not treated at all with ruxolitinib, given a lower dose of ruxolitinib leading to inadequate response, or give a full dose ruxolitinib, which typically leads to need for red blood cell (RBC) transfusions. See e.g., Haematologica. 2016 Dec; 101(12): e482–e484. Patients who have become dependent on RBC transfusions suffer from an even worse quality of life and prognosis. Another unmet medical need is the lack of alternative therapies for treating myelofibrosis. This means that i) those who do not achieve an adequate response to ruxolitinib; ii) those who are intolerant to ruxolitinib; and iii) those who progress despite treatment with ruxolitinib have little or no alternative treatment options and those who despite initial response progress over time (approximately 75% of patients discontinue ruxolitinib due to progression or toxicity).

SUMMARY

[0005] It has now been found that 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, an inhibitor of the Bromodomain and Extra-Terminal (BET) family, is effective in treating myelofibrosis and has numerous advantages over the current standard of care, i.e., ruxolitinib.

[0006] Unlike ruxolitinib, treating myelofibrosic subjects with 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide increased

hemoglobin levels. This is particularly important for subjects who are also anemic. For example, patients 247 and 248 in the Exemplification section below experienced an increase in hemoglobin levels from about 8 g/dL to near normal at about 11.5 g/dL. See e.g., **FIG. 5**. In addition, platelet counts were normalized from about 8 g/dl to about 10.9 g/dl. See e.g., **FIG. 5**.

[0007] Other results showed that uncontrolled thrombocytosis could be alleviated (i.e., platelets were normalized) in a subject that was refractory to all standard of care, including the JAK inhibitor ruxolitinib, following treatment with Compound **1**. See e.g., **FIG. 6** and the Exemplification section below. An improvement in headaches was also found.

[0008] Further results showed transfusion dependence could be reversed following treatment with Compound **1**. For example, the subject who was transfusion dependent while taking the JAK inhibitor ruxolitinib became transfusion independent after undergoing treatment with Compound **1**, and remained transfusion independent for more than 24 weeks. See e.g., **FIG. 5**. Similar results were seen using a combination of both ruxolitinib and 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide. See e.g., Patients 245 and 246 in the Exemplification section below. See e.g., **FIG. 6**.

[0009] As an additional advantage, 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide significantly decreased spleen size, even in subjects who were resistant to ruxolitinib. For example, prior to administration of Compound **1**, Patient 245 as described below became resistant to ruxolitinib with her spleen increasing 25% in size (spleen volume was 12 cm by palpation). However, after 4 weeks of therapy with Compound **1** and ruxolitinib, her spleen size was reduced to 5 cm.

[0010] Provided herein therefore are methods of using 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, alone or in combination with a JAK inhibitor such as ruxolitinib, to treat myelofibrosis.

[0011] In certain aspects, also provided herein are methods of using 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, alone or in combination with a JAK inhibitor such as ruxolitinib, to treat myelofibrosis in subjects with anemia.

BRIEF DESCRIPTION OF THE FIGURES

[0012] **FIG. 1** shows the effects of Compound **1** on *IL6* and *IL10* mRNA transcript levels.

[0013] **FIG. 2** depicts histograms of Compound **1** effect on megakaryocyte differentiation.

[0014] **FIG. 3** represents the histograms and quantitation of effects on mature megakaryocyte marker CD42b after Treatment with Compound **1** and ruxolitinib for 10 days in stem-cell derived megakaryocyte cultures from healthy donor 2 where the grey histrogram is DMSO treated sample, blue histogram is Compound **1** treated sample, and CD42b high calculations refer to the Compound **1**-treated samples.

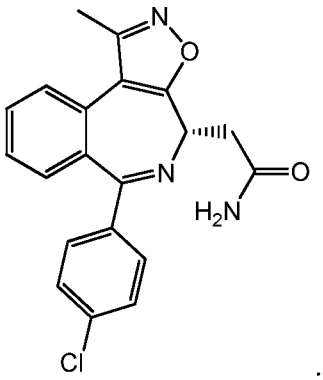
[0015] **FIG. 4** shows the repression of BET-target genes IL8 and CCR1 in circulating blood 2 hours post-dose as a function of the plasma concentration of Compound **1**.

[0016] **FIG. 5** shows the changes in hemoglobin levels and transfusion requirements in a combination arm of Compound **1** and ruxolitinib.

[0017] **FIG. 6** shows the change in platelet and hemoglobin levels in patient 247 of the monotherapy arm.

DETAILED DESCRIPTION

[0018] 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is exemplified as Compound 144 in U.S. Patent No. 8,796,261, the entire contents of which are incorporated herein by reference. 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide is used interchangeably herein with Compound **1**, and is represented by the following structural formula:



Crystalline forms of Compound **1** are disclosed in U.S. 9,969,747, the entire contents of which are incorporated by reference herein.

[0019] Compound **1** is a potent and selective small molecule designed to promote anti-tumor activity by selectively inhibiting the function of BET protein. See e.g., J. Med. Chem., 2016; Feb. 25; 59(4): 1330-9. Compound **1** is being investigated for its profound effects in treating hematological malignancies including progressive lymphoma. See e.g., U.S. Clinical Trials NCT02157636 and NCT01949883. It has now been found, however, that Compound **1**

is also effective in treating myelofibrosis. To this end, for example, Compound **1** increased hemoglobin levels, normalized platelet counts, and reduced spleen size. Subjects who were previously transfusion dependent became transfusion independent after treatment.

[0020] Therefore, in a first embodiment, provided herein is a method of treating myelofibrosis in a subject comprising administering to the subject a therapeutically effective amount of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof. Also provided is the use of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating myelofibrosis in a subject. Further provided is 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, for treating myelofibrosis in a subject.

[0021] The terms "subject" and "patient" may be used interchangeably, and mean a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

[0022] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, reducing the likelihood of developing, or inhibiting the progress of myelofibrosis, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed, *i.e.*, therapeutic treatment. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors), *i.e.*, prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence. Symptoms specific to myelofibrosis include, but are not limited to, abdominal discomfort, dyspnea on exertion, early satiety, fatigue, headaches, night sweats, dizziness, fever, chills, insomnia, pruritus, or bone pain.

[0023] As detailed in the Exemplification section below, Compound **1** was effective in subjects who have undergone treatment for myelofibrosis with JAK inhibitors such as ruxolitinib. Therefore, in a second embodiment, provided herein is a method of treating myelofibrosis in a subject comprising administering to the subject a therapeutically effective amount of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, wherein the subject has

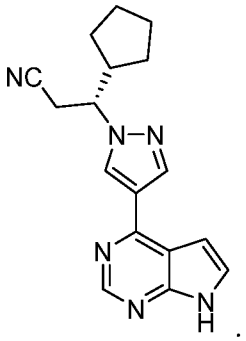
previously undergone treatment with a janus kinase (JAK) inhibitor (e.g., ruxolitinib). Also provided is the use of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating myelofibrosis in a subject who has previously undergone treatment with janus kinase (JAK) inhibitor (e.g., ruxolitinib). Further provided is 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, for treating myelofibrosis in a subject who has previously undergone treatment with a janus kinase (JAK) inhibitor (e.g., ruxolitinib).

[0024] In a third embodiment, the subjects described in the first and second embodiments are characterized as progressed/relapsed to a JAK inhibitor. In a fourth embodiment, the subjects described in the first and second embodiments are characterized is refractory/resistant to a JAK inhibitor.

[0025] A subject who is characterized as progressed/relapsed is one who at one time responded to treatment with a JAK inhibitor (e.g., ruxolitinib), but who no longer responds. A subject who is characterized as refractory/resistant is one who is unresponsive or demonstrates worsening of disease while on treatment with a JAK inhibitor (e.g., ruxolitinib).

[0026] Compound **1** was also shown to be effective as a combination treatment with the JAK inhibitor ruxolitinib. Therefore, in a fifth embodiment, provided herein is a method of treating myelofibrosis in a subject comprising administering to the subject a therapeutically effective amount of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a therapeutically effective amount of a janus kinase (JAK) inhibitor (e.g., ruxolitinib), or a pharmaceutically acceptable salt of any of the foregoing. Also provided is the use of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a janus kinase (JAK) inhibitor (e.g., ruxolitinib), or a pharmaceutically acceptable salt of any of the foregoing, in the manufacture of a medicament for treating myelofibrosis in a subject. Further provided is 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a janus kinase (JAK) inhibitor (e.g., ruxolitinib), or a pharmaceutically acceptable salt of any of the foregoing, for treating myelofibrosis in a subject.

[0027] As used herein, ruxolitinib refers to the JAK inhibitor (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate having the following formula.



[0028] The term "effective amount" or "therapeutically effective amount" are used interchangeably and include an amount of a compound described herein that will elicit a desired medical response in a subject having myelofibrosis, e.g., reducing the symptoms of and/or slowing the progression of the disease.

[0029] In a sixth embodiment, the subject treated by the methods described herein (e.g., as in any one of the first through fifth embodiments) is cytopenic. Cytopenic refers to subjects in which the production of one or more blood cell types ceases or is greatly reduced. Types of cytopenia include e.g., anemia (a deficiency of red blood cells), leukopenia or neutropenia (a deficiency of white blood cells), thrombocytopenia (a deficiency in the platelets), and pancytopenia (a deficiency in all three of red blood cells, white blood cells, and platelet counts).

[0030] In a seventh embodiment, the subject treated by the methods described herein (e.g., as in any one of the first through sixth embodiments) is anemic. A subject of the present disclosure (e.g., as in any one of the first through sixth embodiments) is said to be anemic if their hemoglobin value is less than 13.5 g/dL of blood for a male subject or less than 12.0 g/dL of blood for a female subject. In some aspects, a subject (e.g., as in any one of the first through sixth embodiments) is defined herein as being anemic if their hemoglobin value is less than 10.0 g/dL. Subjects treatable by the present methods (e.g., as in any one of the first through sixth embodiments) therefore include those having hemoglobin values less than 13.0 g/dL, less than 12.5 g/dL, less than 12.0 g/dL, less than 11.5 g/dL, less than 11.0 g/dL, less than 10.5 g/dL, less than 10.0 g/dL, less than 9.5 g/dL, less than 9.0 g/dL, or less than 8.5 g/dL for male subjects and less than 11.5 g/dL, less than 11.0 g/dL, less than 10.5 g/dL, less than 10.0 g/dL, less than 9.5 g/dL, less than 9.0 g/dL, or less than 8.5 g/dL for female subjects. In others aspects, a subject (e.g., as in any one of the first through sixth embodiments) is defined herein as being anemic if their hemoglobin value ranges from 7.5 g/dL of blood to 13.5 g/dL of blood for a male subject or from 7.5 g/dL of blood to 12.0 g/dL of blood for a female subject. In others aspects, a subject (e.g., as in any one of the first

through sixth embodiments) is defined herein as being anemic if their hemoglobin value ranges from 7.5 g/dL of blood to 10.5 g/dL of blood for a male subject or from 7.5 g/dL of blood to 10.5 g/dL of blood for a female subject. In others aspects, a subject (e.g., as in any one of the first through sixth embodiments) is defined herein as being anemic if their hemoglobin value ranges from 7.5 g/dL of blood to 10.0 g/dL of blood for a male subject or from 7.5 g/dL of blood to 10.0 g/dL of blood for a female subject. In others aspects, a subject (e.g., as in any one of the first through sixth embodiments) is defined herein as being anemic if their hemoglobin value ranges from 7.7 g/dL of blood to 10.7 g/dL of blood for a male subject or from 7.7 g/dL of blood to 10.5 g/dL of blood for a female subject. In others aspects, a subject (e.g., as in any one of the first through sixth embodiments) is defined herein as being anemic if their hemoglobin value ranges from 7.7 g/dL of blood to 10.0 g/dL of blood for a male subject or from 7.7 g/dL of blood to 10.0 g/dL of blood for a female subject.

[0031] In an eighth embodiment, subjects treated by the methods described herein (e.g., as in any one of the first through seventh embodiments) are thrombocytopenic. A subject of the present disclosure (e.g., as in any one of the first through seventh embodiments) is said to be thrombocytopenic if their platelet count is less than 150,000 platelets/μL of blood. Subjects treatable by the present methods (e.g., as in any one of the first through seventh embodiments) therefore include those having platelet levels less than 140,000 platelets/μL, less than 130,000 platelets/μL, less than 120,000 platelets/μL, less than 110,000 platelets/μL, less than 100,000 platelets/μL, less than 90,000 platelets/μL, less than 80,000 platelets/μL, less than 70,000 platelets/μL, less than 60,000 platelets/μL or less than 50,000 platelets/μL, alone or in combination with one or more of the hemoglobin values described above.

[0032] In a ninth embodiment, subjects treated by the methods described herein (e.g., as in any one of the first through seventh embodiments) are thrombocytemic. A subject of the present disclosure subjects treated by the methods described herein (e.g., as in any one of the first through seventh embodiments) is said to be thrombocytemic if their platelet count is more than 450,000 platelets/μL of blood. Subjects treatable by the present methods (e.g., as in any one of the first through seventh embodiments) therefore include those having platelet levels more than 450,000 platelets/μL, more than 500,000 platelets/μL, more than 550,000 platelets/μL, or more than 600,000 platelets/μL, alone or in combination with one or more of the hemoglobin values described above.

[0033] In a tenth embodiment, the subject treated by the methods described herein (e.g., as in any one of the first through ninth embodiments) is leukopenic. A subject (e.g., as in any

one of the first through ninth embodiments) is said to be leukopenic if their white blood cell (WBC) count is less than 4,000 WBCs/μL of blood. In certain aspects, subjects treatable by the present methods (e.g., as in any one of the first through ninth embodiments) include those having WBC counts of less than 3,500 WBCs/μL, 3,200 WBCs/μL, 3,000 WBCs/μL, or 2,500 WBCs/μL, alone or in combination with one or more of the hemoglobin and/or platelet values described above.

[0034] In an eleventh embodiment, the subject treated by the methods described herein is (e.g., as in any one of the first through tenth embodiments) neutropenic. In one aspect, a subject of the present disclosure (e.g., as in any one of the first through tenth embodiments) is said to be neutropenic if their neutrophil count is less than 1500 neutrophils/μL of blood. In certain aspects, subjects treatable by the present methods (e.g., as in any one of the first through tenth embodiments) include those having neutrophil counts of less than 1250 neutrophils/μL, 1000 neutrophils/μL, 750 neutrophils/μL, or 500 neutrophils/μL, alone or in combination with one or more of the hemoglobin, platelet, and/or WBC values described above.

[0035] Myelofibrosis is often associated with an enlarging of the spleen. Enlarging of the spleen can result in a feeling of fullness, indigestion, and a loss of appetite. In a twelfth embodiment, subjects treatable by the present methods (e.g., as in any one of the first through eleventh embodiments) include those having an enlarged spleen or liver.

[0036] In a thirteenth embodiment, subjects treatable by the present methods (e.g., as in any one of the first through twelfth embodiments) may also be experiencing one or more additional symptoms. These symptoms include, but are not limited to, abdominal discomfort, dyspnea on exertion, early satiety, fatigue, headaches, night sweats, dizziness, insomnia, pruritus, or bone pain.

[0037] In a fourteenth embodiment, subjects treated by the present methods (e.g., as in any one of the first through thirteenth embodiments) are transfusion dependent prior to treatment with Compound **1**. In some aspects, "transfusion dependent" means that a subject requires red blood cell (RBC) transfusions in order to maintain an acceptable level of hemoglobin. An acceptable level of hemoglobin is determined by those skill in the art and can range from e.g., from 13.5 to 17.5 g/dL of blood for men and from 12.0 to 15.5 g/dL of blood in women. It will be understood that subjects undergoing treatment with rux may have lower hemoglobin levels than those described above and still be deemed an "acceptable" level in order for treatment to continue.

[0038] The compounds of the methods described herein can be formulated as pharmaceutical compositions and administered to a subject, such as a human, in a variety of forms adapted to the chosen route of administration. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, buccal, transdermal, inhalation, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrathecal, intrasternal injection or infusion techniques. Methods of formulating pharmaceutical compositions are well known in the art, for example, as disclosed in "Remington: The Science and Practice of Pharmacy," University of the Sciences in Philadelphia, ed., 21st edition, 2005, Lippincott, Williams & Wilkins, Philadelphia, PA.

[0039] Pharmaceutical compositions of the invention can be prepared by combining a compound of the methods described herein with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Thus, the present compounds of the methods described herein may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable excipient such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[0040] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the composition. In one aspect, however, when used as a monotherapy (i.e., without a JAK inhibitor such as ruxolitinib) Compound **1**, or a pharmaceutically acceptable salt thereof, may be formulated at a dose of from 50 mg to 500 mg for e.g., administration once, twice, or three times daily. For example, in monotherapies, Compound **1** may be administered at a dosage of from 100 mg to 300 mg/day, from 150 mg to 250 mg/day, or at 150 mg/day, 175 mg/day, 200 mg/day, 225 mg/day, or 250 mg/day. In other aspects, when used in combination with a JAK inhibitor such as ruxolitinib, Compound

1, or a pharmaceutically acceptable salt thereof, may be formulated at a dose of from 50 mg to 500 mg for e.g., administration once, twice, or three times daily. For example, in combination therapies, Compound **1** may be administered at a dosage of from 100 mg to 300 mg/day, from 100 mg to 200 mg/day, or at 100 mg/day, 125 mg/day, 150 mg/day, 175 mg/day, or 200 mg/day.

EXEMPLIFICATION

[0041] Compound **1** can be obtained following the procedures describe in U.S. Patent No. 8,796,261 and WO 2015/195862, both of which are incorporated herein by reference.

Inhibitory Effect on Cytokine Release In Vitro

[0042] Compound **1** was assessed for its ability to suppress the expression of NF-κB target genes in two experiments. In one experiment, THP-1 acute leukemia cell lines were exposed to lipopolysaccharide treatment and then Compound **1** for 16 hours. IL6 release from the THP-1 acute leukemia cells was inhibited, with an IC_{50} of 0.069 μM. In the other experiment, the ability of Compound **1** to suppress both *IL6* and *IL10* expression in TMD8 ABC-DLBCL cells was investigated (data on file). TMD8 cells were incubated with DMSO or 1.6 μM Compound **1** for 6 or 24 hours. RNA was then extracted from the cells and quantified using qRT-PCR. As shown in **FIG. 1**, Compound **1** substantially suppressed mRNA transcription of both *IL6* and *IL10* after 6 and 24 hours of treatment.

Effect of Compound **1** as a Single Agent on Megakaryocyte Differentiation

[0043] The effects of Compound **1** on megakaryocyte differentiation and proliferation were evaluated using CD34+ cells isolated from healthy donor bone marrow (data on file). The CD34+ cells were grown in megakaryocyte differentiation serum-free stem cell differentiation base medium with a megakaryocyte-driving cytokine cocktail for 14 days with DMSO or Compound **1** at concentrations ranging from 3 nM to 500 nM. The cells were then stained for CD34 (progenitor marker), CD45 (leukocyte marker) and CD41a (mature megakaryocyte marker) and assessed by FACS for viability and marker expression. CD41a expression and cell size were used as markers of megakaryocyte differentiation. Compound **1** reduced the number of cells with high CD41a expression in a concentration-dependent manner. The shift from high to low CD41a expression began at approximately 50 nM, with pronounced effects observed at 200 to 500 nM, as shown in **FIG. 2**. The loss of CD41a-high-expressing cells suggests impaired megakaryocyte differentiation and loss of mature megakaryocytes.

Effects of Compound **1** Alone and in Combination with Ruxolitinib on Megakaryocyte Differentiation and Proliferation

[0044] In a similar experiment, CD34+ cells that were isolated from the bone marrow of two healthy donors were incubated for 10 days in megakaryocyte differentiation media with DMSO; Compound **1** alone, at a concentration of 30 to 500 nM; ruxolitinib alone at concentration of 8 to 1000 nM; or Compound **1** in combination with ruxolitinib at the same concentrations they were tested alone (data on file). The cells were then harvested for FACS analysis with live/dead stain and gating with CD34 (progenitor marker) and CD41a and CD42b (mature megakaryocyte markers). While Compound **1** showed limited effects on overall viability (percent of live cells by live/dead stain), it demonstrated potent effects on overall cell proliferation (total live count) and megakaryocyte differentiation (percent of cells double positive for CD41a and CD42b), which led to an overall loss of live mature megakaryocytes (mean EC_{50} of 28 nM; **Table 1**).

[0045] In contrast to Compound **1**, ruxolitinib exerted effects on megakaryocyte differentiation at a similar concentration that killed the progenitor cells (mean EC_{50} values of 526 and 644 nM, respectively; **Table 1**), suggesting the inhibitory effects of ruxolitinib on megakaryocytes are based on its cytotoxicity. When serial dilutions of Compound **1** were combined with serial dilutions of ruxolitinib, an additive inhibitory effect was observed on megakaryotcyte differentiation (**FIG. 3**). A similar additive effect was seen on overall cell proliferation where the mean EC_{50} for Compound **1** decreased from 38 to 17 nM (extrapolated), below the lowest dose tested in the presence of 250 nM ruxolitinib, indicating that concentrations of Compound **1** and ruxolitinib near their IC_{50} values for megakaryocyte differentiation and proliferation were effective at reducing the quantity of the other agent needed to elicit the same effect.

Table 3: Compound 1 EC50 values following 10 days of treatment of CD34+ cells

Parameter	Compound 1 EC_{50} (nM)			Ruxolitinib EC_{50} (nM)		
	Donor 1	Donor 2	Mean	Donor 1	Donor 2	Mean
Viability	300	>500	400	676	611	644
Total live count	43	32	38	288	259	274
Megakaryocyte differentiation	60	131	96	517	535	526
Megakaryocyte live count	26	29	28	312	258	285

Reduction in Cytokine Levels in Peripheral Blood

[0046] A panel of selected BET target genes (*CCR1, CCR2, IL8, FN1, CSF1R and THBS1)* was evaluated in peripheral blood samples from patients participating in the Compound **1** Phase 1 clinical studies, in order to determine the relationship between systemic exposure of Compound **1** and suppression of these BET inhibitor-sensitive genes. Gene expression analysis, along with the Compound **1** plasma concentration versus time data, shows that there is a time- and concentration-dependent relationship. Consistent with non-clinical data, Compound **1**-induced changes in expression were most consistently observed for *IL8* and *CCR1* at 2 hours post treatment, indicating the rapid effects of BET inhibition on transcription. Examples of the exposure-response relationships for *CCR1* and *IL8* are presented in **FIG. 4**. The data shown includes samples taken from patients with lymphoma who were treated with Compound **1** in Study 0610-01. Gene expression values were normalized to those measured at a single time point pre-treatment (100%). This data demonstrated the rapid on-target effects of BET inhibition on key pro-inflammatory genes and supports the use of this clinical biomarker assay.

Clinical Signs of Activity in Patients with Myelofibrosis

[0047] The first four myelofibrosis patients who enrolled in Study 0610-02 have demonstrated clinical benefit that as of July 2018 had extended at least 6 months. The first two myelofibrosis patients to enroll (Patients 245 and 246) received Compound **1** in combination with ruxolitinib and have received 18 treatment cycles (11 months of treatment) as of this writing. The next two patients to enroll (Patients 247 and 248) have received 10 cycles of Compound **1** as monotherapy (6 months of treatment) so far. All four patients remain on treatment and have experienced a reduction in their constitutional symptoms, a decrease in spleen volume and an increase in hemoglobin. The single patient who was transfusion dependent at study entry became transfusion independent (defined as >12 weeks without the need for a red blood cell (RBC) transfusion (as of July 2018, 7 months had elapsed since their last transfusion). Their most recent hemoglobin measurement was 10.9g/dL. Consistent with this finding, all four patients have experienced an increase in their hemoglobin levels with multiple treatment cycles with Compound **1**. In addition, the one patient who entered the study with uncontrolled thrombocytosis (baseline platelets were 895 $\times 10^9$/L experienced a normalization of their platelet counts within the first month of monotherapy treatment with Compound **1** that has been maintained (most recent platelet measurement was 132 $\times 10^9$/L). Platelets recovery was associated with significant

improvement in headaches. Brief narratives for all four patients treated for at least 6 months are presented below.

Combination Therapy Arm

[0048] Patient 245, a 66 year-old female was diagnosed with myelofibrosis in May 2014, remained treatment naïve until January 2016 when she initiated treatment with ruxolitinib 15 mg twice daily (BID). Panobinostat was added in February 2016 and discontinued in March 2017, due to the development of anemia. From March 2017, while on ruxolitinib alone, the patient became resistant to ruxolitinib, with her spleen increasing 25% in size.

[0049] At entry into Study 0610-02 in July 2017, the spleen volume of Patient 245 by MRI was 1404 cc and was 12 cm by palpation. The patient presented with early satiety, night sweats, and dyspnea at the start of the study. Within 4 months of treatment with Compound **1**, 125 mg QD and ruxolitinib 15 mg BID, the patient had resolution of early satiety; her spleen was 5 cm by palpation and her liver was no longer palpable. The lowest spleen volume by MRI was 1144 cc, a 19% reduction, at the 6-month MRI. The dose of ruxolitinib was reduced on Cycle 10 to 7.5 mg BID to address decreasing platelet count. Her platelets counts have gradually improved following the dose reduction of ruxolitinib; however still remain below the protocol-specified criteria of 100×10^9/L for two treatment cycles to permit a dose increase in Compound **1**. The patient has otherwise been doing well, with no substantive changes in her symptoms.

[0050] Patient 246 is a 53 year-old female who was diagnosed with myelofibrosis in 2009. During 2002 and 2006, the patient cycled between epoetin alfa, lenalidomide and thalidomide then received lenalidomide for 7 years until 2013. She required RBC transfusions during 2013 and initiated interferon in 2014, which allowed her to become transfusion independent. Interferon was discontinued almost a year later due to fatigue. The patient remained transfusion independent and without further treatment until late 2016 when they once again became transfusion dependent. Ruxolitinib 5 mg BID was started in January 2017. Ruxolitinib was increased to 10 mg BID in April 2017, but the patient remained transfusion dependent and symptomatic. She was considered ruxolitinib resistant due an increasing spleen size and exacerbated symptoms (extreme fatigue, shortness of breath, distress on exertion, occasional nausea and night sweats) while on ruxolitinib therapy.

[0051] When Patient 246 initiated combination treatment with Compound **1** 125 mg QD and ruxolitinib 10 mg BID in July 2017 her spleen volume was 607 cc by MRI and 2 cm by palpation and she required regular transfusions (2 units of RBC every 3-4 weeks). The dose

of Compound **1** was titrated up to 175 mg QD after five treatment cycles and within 7 months of combination therapy, the patient had become transfusion independent (defined as >12 weeks without a transfusion and hemoglobin > 8 g/dL; see **FIG. 5**), which has been maintained for >30 weeks (most recent hemoglobin measurement was 10.9g/dL). She has also experienced a clinically meaningful improvement in her associated constitutional symptoms (fatigue and dyspnea) and has had an incremental decrease in spleen volume, achieving a 37% reduction in spleen volume by Cycle 12 (380 cc).

Monotherapy Arm

[0052] Patient 247 is a 46 year-old female who was diagnosed with myelofibrosis in April 2014. In 2009, it was suspected that the patient had essential thrombocytosis (ET) for which she received hydroxyurea treatment from April 2009 to December 2017. The patient also received one month of epoetin alpha in 2015, three months of imetelstat in 2016 and four months of pembrolizumab in 2017. Ruxolitinib was administered from October 2015 to May 2016. Ruxolitinib was discontinued due to worsening symptomatic splenomegaly, anemia, leukocytosis, and thrombocytosis.

[0053] Upon entry into Study 0610-02 in December 2017, Patient 247 had a spleen volume of 858 cc by MRI and 5 cm by palpation and a host of constitutional symptoms, including: abdominal discomfort, dyspnea on exertion, early satiety, fatigue, headaches, night sweats, dizziness, insomnia, pruritus, and bone pain. The patient also presented with uncontrolled thrombocytosis at study entry (platelet count of 895 $\times 10^9$/L at baseline) despite hydroxyurea. In addition, the patient had experienced persistent and debilitating headaches that required multiple hospital admissions for pain control. Their platelets were normalized after receiving their first two weeks of Compound **1** monotherapy (183 $\times 10^9$/L) and have remained within the normal range for the remainder of the time they have been on study (see **FIG. 6**). Within 2 months on Compound **1** monotherapy, the patient's severe headaches had resolved; their night sweats were less frequent; and a 37% reduction in symptoms was assessed by the Myeloproliferative Neoplasm Symptom (MNS) score. Their ECOG performance score decreased from 2 to 1 after two treatment cycles with CPI-0610 and a 25% decrease in spleen volume (640 cc) was assessed by MRI after 8 treatment cycles, the most recent measurement.

[0054] Patient 248, a 76 year-old male who was diagnosed with myelofibrosis in September 2011 was treated with fresolemunib (December 2011 to October 2012) and itacitinib (December 2012 to July 2014). Ruxolitinib 5 mg BID was initiated in January 2015

and increased to 15 mg BID in December 2015. Ruxolitinib was discontinued in September 2016 because the patient was experiencing generally worsening fatigue, anemia and thrombocytopenia. Subsequent to ruxolitinib treatment, the patient received imetalstat from June 2016 through March 2017, followed by pembrolizumab from June to October 2017.

[0055] In December 2017, Patient 248 initiated CPI-0610 monotherapy in Study 0610-02. At that time, the patient had a spleen volume of 1148 cc by MRI and 5 cm by palpation. Their constitutional symptoms at study entry included fatigue, early satiety, and difficulty concentrating. The patient did not tolerate the 225 mg QD starting dose of CPI-0610 (he experienced nausea, diarrhea, malaise and dizziness), requiring dose interruption after the first 5 doses of Cycle 1. The patient was reinitiated with a reduced Compound **1** dose of 175 mg at the beginning of Cycle 2, which has been tolerated for the remaining time on study (>6 months). While the patient's spleen has shown minimal change through palpation a spleen volume reduction of 11% (1023 cc) was measured by MRI after 3 months on treatment with CPI-0610. Their MNS score improved 19% after 2 months on the 175 mg QD dose and after 6 months of Compound **1** treatment his bone marrow fibrosis grade decreased from MF-2 at baseline to MF-1 based on a local pathologist's assessment.

[0056] While have described a number of embodiments of this, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this disclosure. Therefore, it will be appreciated that the scope of this disclosure is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

[0057] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

1. A method of treating myelofibrosis in a subject comprising administering to the subject a therapeutically effective amount of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1, wherein the subject has previously undergone treatment with a janus kinase (JAK) inhibitor.

3. The method of Claim 1 or 2, wherein the subject is progressed/relapsed to a JAK inhibitor.

4. The method of Claim 1 or 2 wherein the subject is refractory/resistant to a JAK inhibitor.

5. The method of any one of Claims 1 to 4, wherein the subject has previously undergone treatment with ruxolitinib.

6. A method of treating myelofibrosis in a subject comprising administering to the subject a therapeutically effective amount of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide and a therapeutically effective amount of a janus kinase (JAK) inhibitor, or a pharmaceutically acceptable salt of any of the foregoing.

7. The method of Claim 6, wherein the JAK inhibitor is ruxolitinib.

8. The method of any one of Claims 1 to 7, wherein the subject is cytopenic.

9. The method of any one of Claims 1 to 8, wherein the subject is anemic.

10. The method of any one of Claims 1 to 9, wherein the subject has a hemoglobin count of less than 10 g/dL.

11. The method of any one of Claims 1 to 10, wherein the subject is thrombocytopenic.

12. The method of any one of Claims 1 to 11, wherein the subject's platelet count is less than 120,000 platelets/μL.

13. The method of any one of Claims 1 to 10, wherein the subject is thrombocytemic.

14. The method of any one of Claims 1 to 10 and 13, wherein the subject's platelet count is more than 500,000 platelets/μL.

15. The method of any one of Claims 1 to 14, wherein the subject is neutropenic.

16. The method of any one of Claims 1 to 15, wherein the subject's absolute neutrophil count is less than 1000 neutrophils/μL of blood.

17. The method of any one of Claims 1 to 16, wherein the subject has an enlarged spleen or liver.

18. The method of any one of Claims 1 to 17, wherein the subject is suffering from abdominal discomfort, dyspnea on exertion, early satiety, fatigue, headaches, night sweats, dizziness, insomnia, pruritus, or bone pain.

19. The method of any one of Claims 1 to 18, wherein the subject is transfusion dependent.

20. The method of any one of Claims 1 to 5 and 8 to 19, wherein the subject is administered from 100 mg/day to 300 mg/day of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof.

21. The method of any one of Claims 1 to 5 and 8 to 20, wherein the subject is administered from 150 mg/day to 250 mg/day of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof.

22. The method of any one of Claims 6 to 19, wherein the subject is administered from 100 mg/day to 300 mg/day of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof.

23. The method of any one of Claims 6 to 19 and 22, wherein the subject is administered from 100 mg/day to 200 mg/day of 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof.

24. The method of any one of Claims 1 to 23, wherein the subject is administered 2-((4S)-6-(4-chlorophenyl)-1-methyl-4H-benzo[c]isoxazolo[4,5-e]azepin-4-yl)acetamide, or a pharmaceutically acceptable salt thereof, once per day.

.

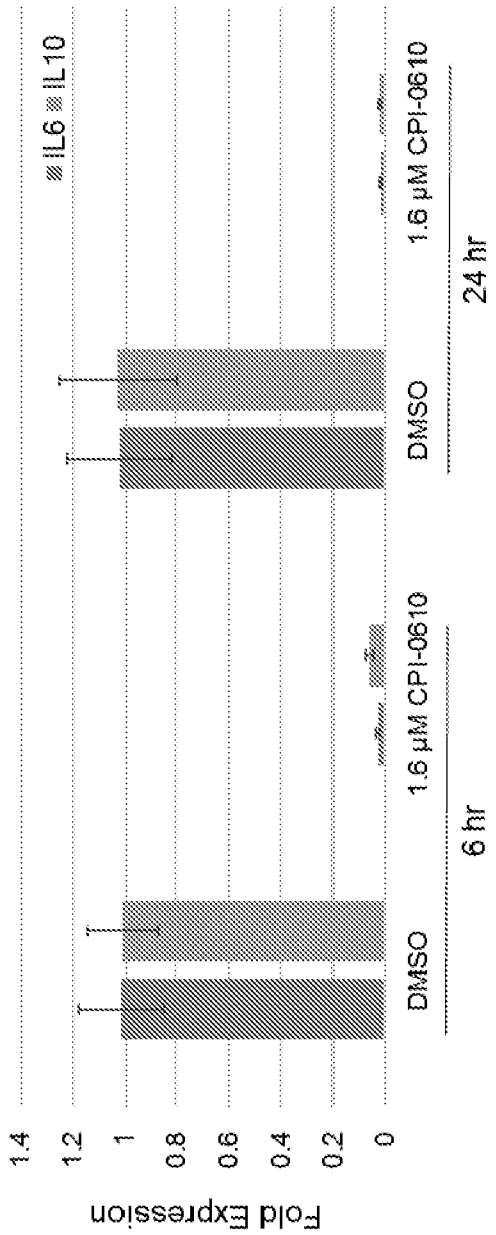
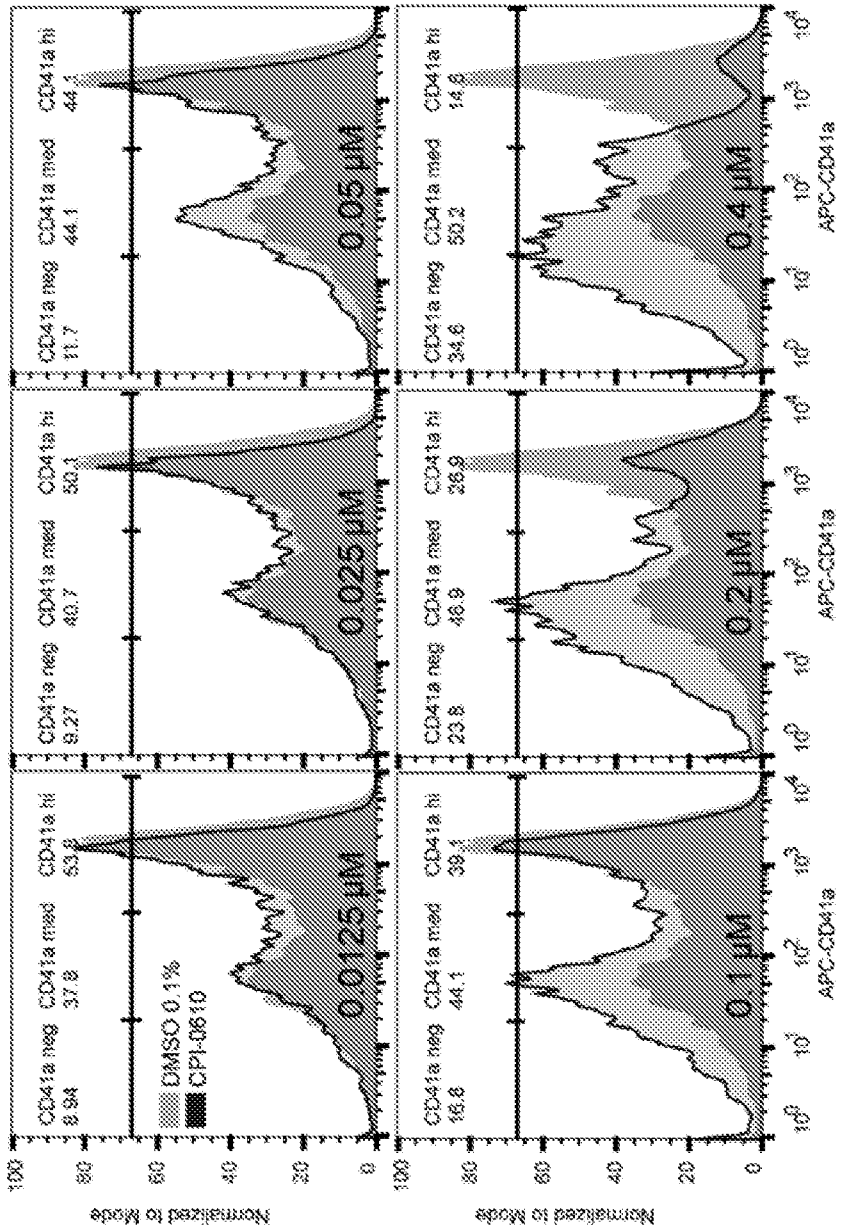

IL6
IL10
Fold Expression
1.4
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
1.6 µM CPI-0610
DMSO
1.6 µM CPI-0610
6 hr
24 hr

FIG. 1

FIG. 2


DMSO 0.1%
CPI-0610
0.0125μM
0.025μM
0.05μM
0.1μM
0.2μM
0.4μM
CD41a neg
CD41a med
CD41a hi
Normalized to Mode
APC-CD41a

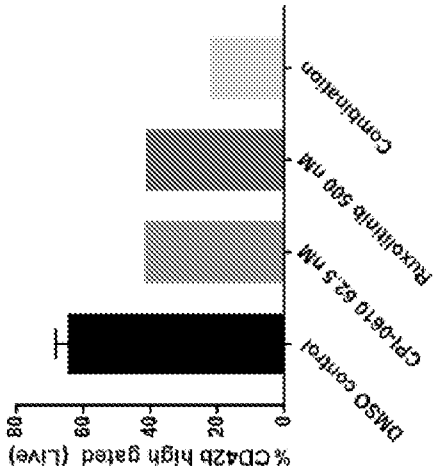
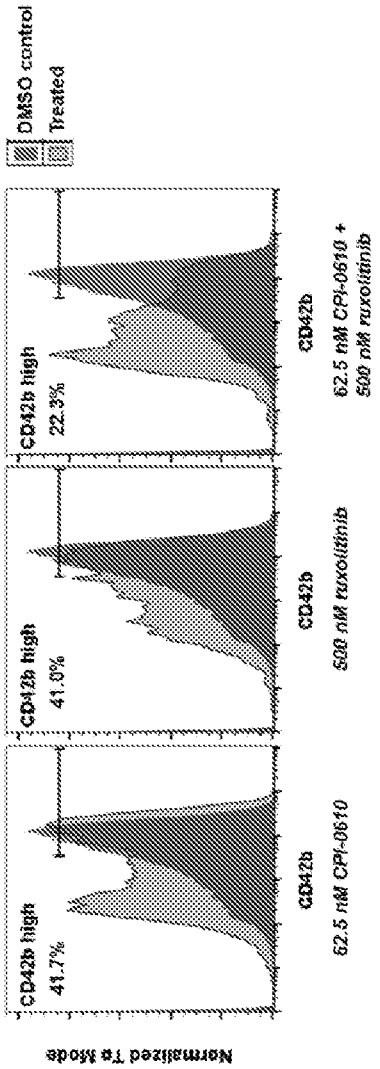

% CD42b high gated (Live)
80
60
40
20
0
DMSO control
CPI-0610 62.5 nM
Ruxolitinib 500 nM
Combination

FIG. 3


DMSO control
Treated
Normalized Tx Mode
CD42b high
41.7%
CD42b
62.5 nM CPI-0610
CD42b high
41.0%
CD42b
500 nM ruxolitinib
CD42b high
22.3%
CD42b
62.5 nM CPI-0610 +
500 nM ruxolitinib

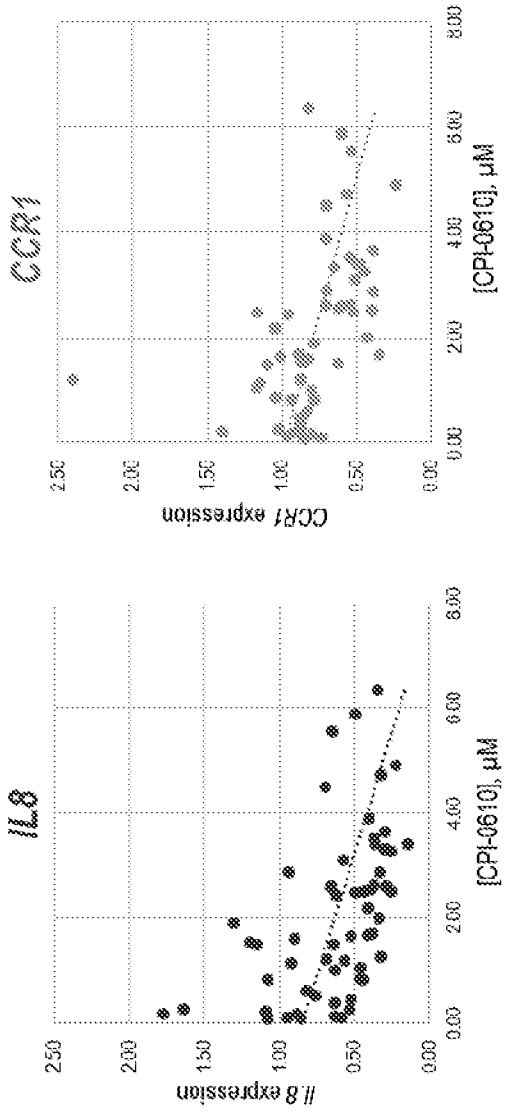

CCR1
CCR1 expression
2.50
2.00
1.50
1.00
0.50
0.00
0.00
2.00
4.00
6.00
8.00
[CPI-0610], µM
IL8
IL8 expression
2.50
2.00
1.50
1.00
0.50
0.00
0.00
2.00
4.00
6.00
8.00
[CPI-0610], µM

FIG. 4

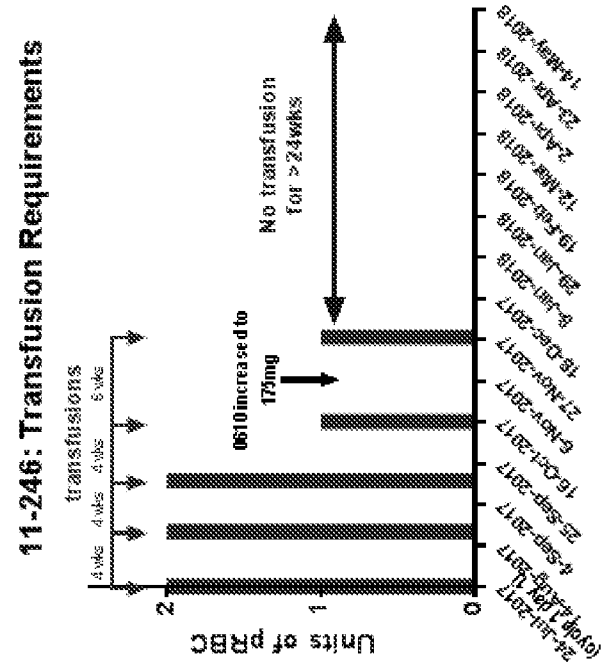
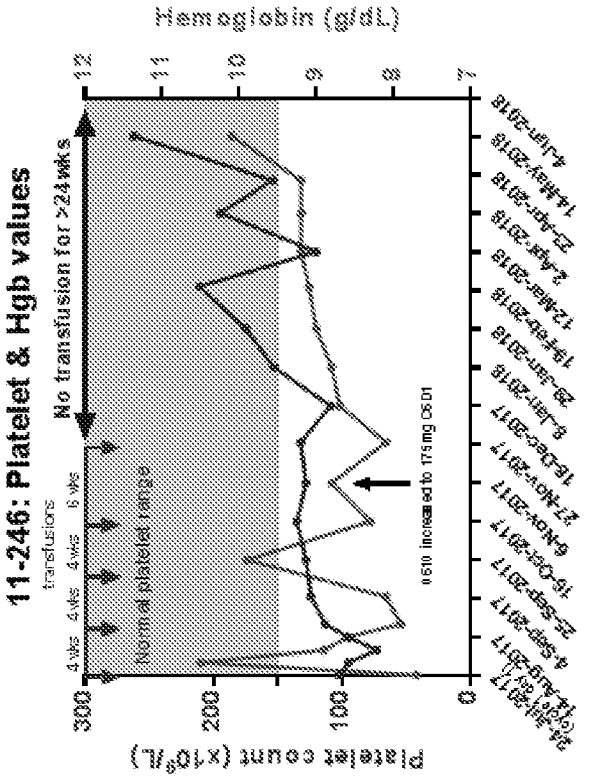

11-246: Transfusion Requirements
transfusions
4 wks
4 wks
4 wks
6 wks
0610increased to 175mg
No transfusion for >24wks
Units of pRBC
0
1
2
24-Jul-2017 (cycle 1 day 1)
4-Sep-2017
25-Sep-2017
16-Oct-2017
6-Nov-2017
27-Nov-2017
18-Dec-2017
8-Jan-2018
29-Jan-2018
19-Feb-2018
12-Mar-2018
2-Apr-2018
23-Apr-2018
14-May-2018

FIG. 5


11-246: Platelet & Hgb values
transfusions
4 wks
4 wks
4 wks
6 wks
No transfusion for >24 wks
Normal platelet range
0610 increased to 175 mg C6 D1
Platelet count (x10⁹/L)
Hemoglobin (g/dL)
0
100
200
300
7
8
9
10
11
12
24-Jul-2017 (cycle 1 day 1)
14-Aug-2017
4-Sep-2017
25-Sep-2017
16-Oct-2017
6-Nov-2017
27-Nov-2017
18-Dec-2017
8-Jan-2018
29-Jan-2018
19-Feb-2018
12-Mar-2018
2-Apr-2018
23-Apr-2018
14-May-2018
4-Jun-2018

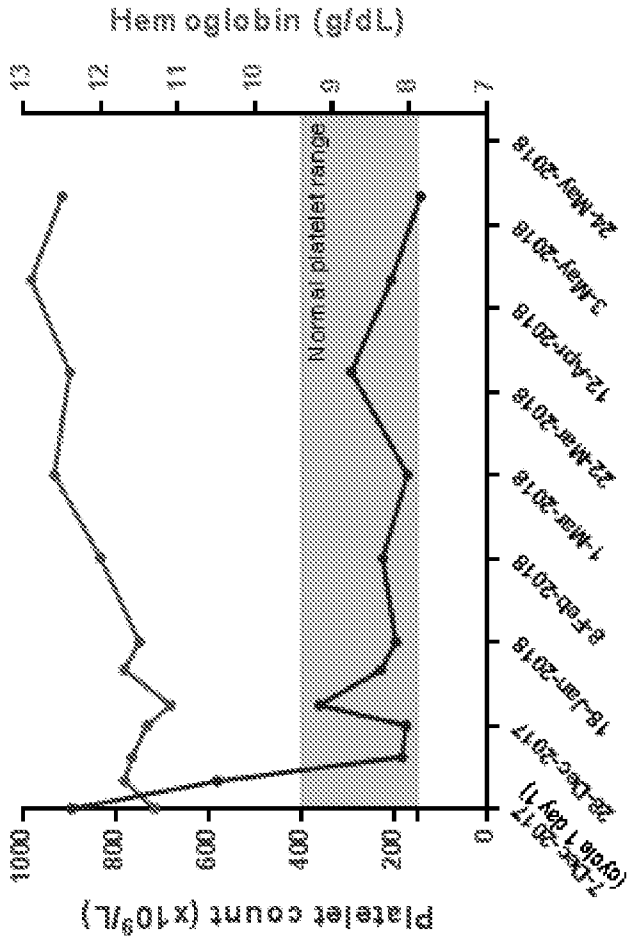
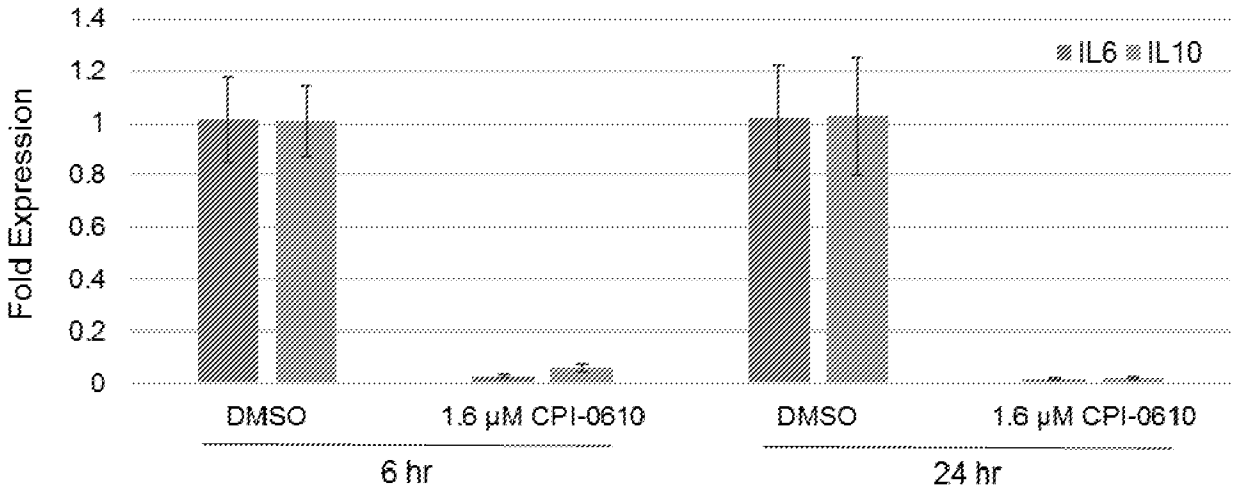

Hemoglobin (g/dL)
13
12
11
10
9
8
7
Normal platelet range
Platelet count (x10⁹/L)
1000
800
600
400
200
0
7-Dec-2017 (Dyoba 1 Day 1)
28-Dec-2017
18-Jan-2018
8-Feb-2018
1-Mar-2018
22-Mar-2018
12-Apr-2018
3-May-2018
24-May-2018

FIG. 6

FIG. 1


1.4
1.2
1
0.8
0.6
0.4
0.2
0
Fold Expression
IL6
IL10
DMSO
1.6 µM CPI-0610
DMSO
1.6 µM CPI-0610
6 hr
24 hr