SUSTAINED-RELEASE DOSAGE FORMS OF RUXOLITINIB

FIELD OF THE INVENTION

The present invention relates to sustained-release formulations and dosage forms of ruxolitinib, or a pharmaceutically acceptable salt thereof, which are useful in the treatment of Janus kinase-associated diseases such as myeloproliferative disorders.

BACKGROUND OF THE INVENTION

Ruxolitinib ((3R)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile) is the first FDA approved Janus kinase (JAK) inhibitor and is the only drug currently approved for treatment of myelofibrosis. Mascarenhas, J. et al. Clin Cancer Res. 2012 Jun 1;18(11):3008-14. Epub 2012 Apr 2. The compound has been shown in the clinic to effectively reduce spleen volume and improve total symptom scores in patients suffering from myelofibrosis. See, e.g., Verstovsek, S., et al. "A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis," N. Eng. J. Med., 2012, Mar 1:366(9):799-807, which is incorporated herein by reference in its entirety, which reports the results of a Phase 3 clinical trial (COMFORT-I Study) of ruxolitinib for myelofibrosis. See also, Harrison, C. et al., "JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis," N. Eng. J. Med., 2012, Mar 1;366(9):787-98 reporting Phase 3 clinical trial results of the COMFORT-II study, which is incorporated herein by reference in its entirety.

To date, all published human clinical data for ruxolitinib relate to dosing of an immediate-release formulation. However, ruxolitinib is a BCS Class I molecule with rapid oral absorption and a short half-life of about 3 hours. See, Shi et al., J. Clin. Pharmacol. 2012 Jun;52(6):809-18. Epub 2011 May 20. These properties result in a high peak/trough plasma concentration ratio in human subjects leading to multiple daily doses for optimal treatment, and potentially contributing to problems with patient compliance and unwanted side effects.

Ruxolitinib therapy is often associated with the adverse events of thrombocytopenia (low platelet count) and anemia (low hemoglobin). Thrombocytopenia is dose-dependent and considered the dose-limiting toxic effect.

Accordingly, there is a need for new and improved formulations of ruxolitinib that not only mitigate adverse side-effects in patients, but still achieve therapeutic efficacy, and also

facilitate administration of the drug such as by reducing the number of doses required to achieve a therapeutic effect. The sustained-release formulations provided herein help meet these and other needs.

SUMMARY OF THE INVENTION

The present invention is directed to a sustained-release dosage form comprising at least one active ingredient which is ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein the ruxolitinib, or pharmaceutically acceptable salt thereof, is present in the dosage form in an amount of about 10 to about 60 mg on a free base basis.

The present invention is further directed to a method of treating a disease associated with JAK activity in a patient in need thereof, comprising administering the sustained-release dosage form of the invention to said patient.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a graph comparing plasma concentrations of ruxolitinib after administration of a single dose of either 25 mg immediate-release or 25 mg sustained-release formulation in fasted, healthy human subjects.

Figure 2 shows a graph comparing spleen volume responders in the COMFORT-I immediate-release formulation study and the sustained-release study.

Figure 3 shows a graph comparing total symptom scores in the COMFORT-I immediate-release formulation study and the sustained-release study.

Figure 4 shows a graph comparing ruxolitinib steady state plasma concentrations in MF patients dosed with 25 mg immediate-release or 25 mg sustained-release formulations.

DETAILED DESCRIPTION

Sustained-Release Dosage Forms

The present invention provides, *inter alia*, an oral, sustained-release dosage form comprising ruxolitinib, or a pharmaceutically acceptable salt thereof, as an active ingredient. The dosage form can contain ruxolitinib, or a pharmaceutically acceptable salt thereof, in an amount of about 10 to about 60 mg, about 10 to about 40 mg, about 20 to about 40 mg, or about 20 to about 30 mg on a free base basis. In some embodiments, the dosage form contains about 10 mg, about 12.5 mg, about 20 mg, about 25 mg, about 30 mg, about 37.5

mg, about 40 mg, about 50 mg, or about 60 mg on a free base basis. In some embodiments, the dosage form contains about 25 mg of ruxolitinib on a free base basis. The phrase "on a free base basis" indicates that the amount of ruxolitinib or salt thereof in the dosage form is measured based on the molecular weight of ruxolitinib free base only, even when the actual active ingredient is a salt of ruxolitinib having a different molecular weight than the free base. For example, the conversion factor for ruxolitinib phosphate salt to free base is 0.7575.

The structure, preparation, and characterization of ruxolitinib, and pharmaceutically acceptable salts thereof, are described in, e.g., US Pat. No. 7,598,257 and US Pat. Pub. No. 2008/0312259, each of which is incorporated herein by reference in its entirety. In some embodiments, the active ingredient is a pharmaceutically acceptable salt of ruxolitinib, such as the maleic acid salt, sulfuric acid salt, or phosphoric acid salt. In some embodiments, the active ingredient is ruxolitinib phosphate (i.e., phosphoric acid salt of ruxolitinib).

The dosage form of the invention comprises a sustained-release formulation of ruxolitinib, or a pharmaceutically acceptable salt thereof. As used herein, "sustained-release" is used as generally understood in the art and refers to a formulation designed to slowly release the active ingredient into a patient after oral administration and to maintain an essentially steady, therapeutically effective plasma level of active ingredient over a relatively long period of time, such as about 8 to about 24 hours or longer.

The dosage forms of the invention include a sustained-release matrix former. Example sustained-release matrix formers include cellulosic ethers such as hydroxypropyl methylcellulose (HPMC, hypromellose) which is a high viscosity polymer. The sustained-release dosage forms of the invention can include, for example, about 10 to about 30%, about 15 to about 25%, or about 18 to about 24 % by weight of hydroxypropyl methylcellulose(s). In some embodiments, the formulation has about 20 % by weight of one or more hydroxypropyl methylcelluloses. In further embodiments, the formulation has about 22 % by weight of one or more hydroxypropyl methyl celluloses. Example hydroxypropyl methylcelluloses include Methocel K15M, Methocel K4M, and Methocel K100LV.

The sustained-release dosage forms of the invention can further include one or more fillers, glidants, disintegrants, binders, or lubricants as inactive ingredients. Fillers can be present in the formulations in an amount of 0 to about 85 % by weight. In some embodiments, the formulation has about 50 to about 80%, about 55 to about 75%, or about 60 to about 70% by weight of filler. Non-limiting examples of fillers include lactose monohydrate, microcrystalline cellulose, starch 1500, and lactose anhydrous, or combinations

thereof. In some embodiments, the filler comprises microcrystalline cellulose, lactose monohydrate, or both.

Lubricants can be present in the dosage forms of the invention in an amount of 0 to about 5% by weight. Non-limiting examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, polyethylene glycol, sodium stearyl fumarate, and glyceryl behenate. In some embodiments, the formulations include magnesium stearate, stearic acid, or both.

Glidants can be present in the dosage forms of the invention in an amount of 0 to about 5% by weight. Non-limiting examples of glidants include talc, colloidal silicon dioxide, and cornstarch. In some embodiments, the glidant is colloidal silicon dioxide.

Disintegrants can be present in the dosage forms of the invention in an amount of 0 to about 10% by weight. Non-limiting examples of disintegrants include croscarmellose sodium, crospovidone, starch, cellulose, and low substituted hydroxypropyl cellulose. Croscarmellose sodium is a preferred disintegrant.

Film-coating agents can be present in an amount of 0 to about 5% by weight. Non-limiting illustrative examples of film-coating agents include hypromellose or polyvinyl alcohol based coating with titanium dioxide, talc and optionally colorants available in several commercially available complete coating systems.

In some embodiments, the dosage form of the invention includes a sustained-release formulation comprising about 12.2% ruxolitinib phosphate, about 20% hydroxypropyl methylcellulose, about 64.3% filler, about 2.5% lubricant, and about 1% glidant, all by weight.

In some embodiments, the dosage form of the invention includes a sustained-release formulation comprising about 12.2% ruxolitinib phosphate, about 22% hydroxypropyl methylcellulose, about 62.3% filler, about 2.5% lubricant, and about 1% glidant, all by weight.

In some embodiments, the dosage form of the invention includes a sustained-release formulation as set out below.

Component	Percentage (wt%)
Ruxolitinib phosphate	12.2
Microcrystalline cellulose, NF	22.0
Hypromellose, USP (Methocel K15M)	4.0
Hypromellose, USP (Methocel K4M)	16.0
Lactose monohydrate, NF	42.3
Colloidal silicon dioxide, NF	1.0

Magnesium stearate, NF	0.5
Stearic acid, NF	2.0

In some embodiments, the dosage form of the invention includes a sustained-release formulation as set out below.

Component	Percentage (wt%)
Ruxolitinib phosphate	12.2
Microcrystalline cellulose, NF	42.3
Hypromellose, USP (Methocel K100LV)	10.0
Hypromellose, USP (Methocel K4M)	12.0
Lactose monohydrate, NF	20.0
Colloidal silicon dioxide, NF	1.0
Magnesium stearate, NF	0.5
Stearic acid, NF	2.0

In some embodiments, the dosage form of the invention includes a sustained-release formulation as set out below.

Component	Percentage (wt%)
Ruxolitinib phosphate	12.2
Microcrystalline cellulose, NF	22.0 – 42.3
Hypromellose, USP (Methocel K100LV)	0 – 10.0
Hypromellose, USP (Methocel K15M)	0 - 4.0
Hypromellose, USP (Methocel K4M)	12.0 – 16.0
Lactose monohydrate, NF	20.0 – 42.3
Colloidal silicon dioxide, NF	1.0
Magnesium stearate, NF	0.5
Stearic acid, NF	2.0

As used herein, the term “dosage form” is meant to refer to a physically discrete unit of sustained-release formulation of the invention to be administered to a patient. Example dosage forms include tablets, caplets, capsules, and the like, containing any of the sustained-release formulations described herein. Dosage forms can further include pharmaceutically acceptable coatings, pigments, or dyes.

The dosage forms of the invention contain a sustained-release formulation that results in the relatively slow release of ruxolitinib once administered, characterized by particular pharmacokinetic parameters different from those of an immediate-release formulation. The sustained-release dosage forms of the invention can minimize potentially harmful spikes in drug plasma concentrations that are associated with immediate-release formulations, and can help provide continuous, steady, and therapeutically effective plasma levels of drug. The

dosage forms of the invention can be administered to a human patient as needed for therapeutic efficacy against the disease being treated, for example, once daily.

In some embodiments, the dosage forms of the invention are administered to fasted patients. As used herein, "fasted" means, in reference to a human patient or subject, that the patient or subject has not ingested food or drink (except water) for at least 3 hours prior to dosing. In some embodiments, patients are fasted for at least 10 hours prior to dosing.

In further embodiments, the dosage forms of the invention are administered to non-fasted human patients or subjects. Bioavailability of ruxolitinib is high (e.g., about 70-80%) and no food effect has been observed in immediate-release dosage forms. Accordingly, it is believed that the pharmacokinetics of ruxolitinib administered as a sustained-release dosage form would not be significantly different in fasted and non-fasted patients.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 700 nM or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 600 nM or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 500 nM or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 400 nM or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 200 to about 700 nM.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 200 to about 600 nM.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 300 to about 500 nM.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 300 to about 400 nM.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results a mean time to peak plasma concentration (T_{max}) of ruxolitinib of about 1.5 hours or more.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean time to peak plasma concentration (T_{max}) of ruxolitinib of about 1.5 hours to about 5 hours.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean time to peak plasma concentration (T_{max}) of ruxolitinib of about 2 hours to about 4 hours.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 10 or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 6 or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 5 or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 4 or less.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 1 to 10.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 2 to 7.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean half-life ($t_{1/2}$) of from about 3.5 hours to about 11 hours.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a mean half-life ($t_{1/2}$) of from about 4 hours to about 8 hours.

In some embodiments, administration of a single dose of a sustained-release dosage form of the invention to a human results in mean bioavailability ($AUC_{0-\infty}$) of ruxolitinib of at least about 3000 nM*h.

In some embodiments, administration of a single dose of a sustained-release dosage form of the invention to a human results in mean bioavailability ($AUC_{0-\infty}$) of ruxolitinib of at least about 3500 nM*h.

In some embodiments, administration of a single dose of a sustained-release dosage form of the invention to a human results in mean bioavailability ($AUC_{0-\infty}$) of ruxolitinib of about 3000 to about 4000 nM*h.

In some embodiments, administration of a single dose of a sustained-release dosage form of the invention to a human results in mean bioavailability ($AUC_{0-\infty}$) of ruxolitinib of about 3100 to about 3800 nM*h.

In some embodiments, the sustained-release dosage form of the invention has a mean relative bioavailability based on AUC of from about 65 % to about 110 % or about 75% to about 95% relative to an immediate release formulation comprising the same amount of ruxolitinib, or a pharmaceutically acceptable salt thereof, in patients. AUC can be, for example, $AUC_{0-\infty}$ (e.g., for a single dose) or AUC_{0-t} where t is a specified time.

As used herein, "mean" when preceding a pharmacokinetic value (e.g. mean C_{max}) represents the arithmetic mean value of the pharmacokinetic value taken from a population of patients unless otherwise specified.

As used herein, "C_{max}" means the maximum observed plasma concentration.

As used herein, "C_{12h}" refers to the plasma concentration measured at 12 hours from administration.

As used herein, "T_{max}" refers to the time at which the maximum blood plasma concentration is observed.

As used herein, "$T_{1/2}$" refers to the time at which the plasma concentration is half of the observed maximum.

As used herein, "AUC" refers to the area under the plasma concentration-time curve which is a measure of total bioavailability.

As used herein, "$AUC_{0-\infty}$" refers to the area under the plasma concentration-time curve extrapolated to infinity.

As used herein, "AUC_{0-t}" refers to the area under the plasma concentration-time curve from time 0 to the last time point with a quantifiable plasma concentration, usually about 12-36 hours.

As used herein, "$AUC_{0-\tau}$" refers to the area under the plasma concentration-time curve from time 0 to the time of the next dose.

As used herein, "Cl/F" refers to oral clearance.

The sustained-release dosage forms of the invention have certain advantages over immediate-release dosage forms. The maintenance of steady, therapeutically effective plasma levels of ruxolitinib afforded by the sustained-release dosage forms of the invention allows for reduced dosing, such as doing only once per day, as opposed to twice or more for immediate-release forms. The reduced dosing can help with patient compliance in their treatment regimen.

In some embodiments, administration of the sustained-release dosage form of the invention to a human results in a therapeutically effective plasma level of ruxolitinib for at least about 8 hours, at least about 10 hours, at least about 12 hours, at least about 18, or at least about 24 hours. In some embodiments, the sustained-release dosage form of the invention maintains a plasma level between about 75 and about 500 nM for at least about 8 hours, at least about 12 hours, or at least about 18 hours. In some embodiments, the sustained-release dosage form of the invention maintains a plasma level between about 100 and about 400 nM for at least about 6 hours or at least about 8 hours.

An additional advantage of the sustained-release dosage form (e.g., containing 25 mg of ruxolitinib phosphate on a free base basis) includes a reduction in unwanted side effects related to thrombocytopenia and anemia while maintaining therapeutic efficacy comparable with an immediate-release dosing regimen, e.g., 15 mg or 20 mg BID. It was not predictable that a sustained-release formulation of ruxolitinib could both maintain therapeutic efficacy and significantly reduce unwanted side effects related to thrombocytopenia or reduced hemoglobin levels. Clinical data related to efficacy and side effects in myelofibrosis patients for both sustained-release and immediate-release dosing is compared in the Examples.

In some embodiments, administration of the sustained-release dosage form of the invention to a human once daily for at least 16 weeks results in a mean decrease in mean base platelet count of no more than about 100 x 10^9/L, no more than about 80 x 10^9/L, no more than about 60 x 10^9/L, or no more than about 40 x 10^9/L.

In some embodiments, administration of the sustained-release dosage form of the invention to a human once daily for at least 16 weeks results in a mean decrease in mean base platelet count of between about 0 x 10^9/L and about 100 x 10^9/L, between about 30 x 10^9/L and about 80 x 10^9/L, or between about 50 x 10^9/L and about 70 x 10^9/L.

In some embodiments, administration of the sustained-release dosage form of the invention to a human once daily for at least 16 weeks results in a mean decrease in mean baseline hemoglobin (Hgb) of no more than about 15 g/L, no more than about 10 g/L, no more than about 8 g/L, or no more than about 6 g/L.

In some embodiments, administration of the sustained-release dosage form of the invention to a human once daily for at least 16 weeks results in a mean decrease in mean baseline hemoglobin (Hgb) of about 0 to about 15 g/L, about 5 to about 15 g/L, about 2 to about 12 g/L, or about 5 to about 12 g/L.

In some embodiments, the platelet counts and hemoglobin levels are measured in patients having received no blood transfusions during the treatment period.

Mean baseline platelet counts and mean baseline hemoglobin levels are typically measured prior to the start of treatment.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Methods

Another aspect of the present invention pertains to methods of treating a JAK-associated disease or disorder in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a sustained-release dosage form of the invention. A JAK-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the JAK, including overexpression and/or abnormal activity levels. A JAK-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating JAK activity.

Examples of JAK-associated diseases include diseases involving the immune system including, for example, organ transplant rejection (*e.g.*, allograft rejection and graft versus host disease).

Further examples of JAK-associated diseases include autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, autoimmune thyroid disorders, chronic obstructive pulmonary disease (COPD), and the like. In some embodiments, the autoimmune disease is an autoimmune bullous skin disorder such as pemphigus vulgaris (PV) or bullous pemphigoid (BP).

Further examples of JAK-associated diseases include allergic conditions such as asthma, food allergies, eszematous dermatitis, contact dermatitis, atopic dermatitis (atropic eczema), and rhinitis. Further examples of JAK-associated diseases include viral diseases such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV) and Human Papilloma Virus (HPV).

Further examples of JAK-associated disease include diseases associated with cartilage turnover, for example, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, Tietze syndrome, costal athropathy, osteoarthritis deformans endemica, Mseleni disease, Handigodu disease, degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma, or ankylosing spondylitis.

Further examples of JAK-associated disease include congenital cartilage malformations, including hereditary chrondrolysis, chrondrodysplasias, and pseudochrondrodysplasias (e.g., microtia, enotia, and metaphyseal chrondrodysplasia).

Further examples of JAK-associated diseases or conditions include skin disorders such as psoriasis (for example, psoriasis vulgaris), atopic dermatitis, skin rash, skin irritation, skin sensitization (*e.g.*, contact dermatitis or allergic contact dermatitis). For example, certain substances including some pharmaceuticals when topically applied can cause skin sensitization. In some embodiments, co-administration or sequential administration of at least one JAK inhibitor of the invention together with the agent causing unwanted sensitization can be helpful in treating such unwanted sensitization or dermatitis. In some embodiments, the skin disorder is treated by topical administration of at least one JAK inhibitor of the invention.

In further embodiments, the JAK-associated disease is cancer including those characterized by solid tumors (*e.g.*, prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, uterine leiomyosarcoma, melanoma etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute

lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma. Example CTCLs include Sezary syndrome and mycosis fungoides.

In some embodiments, the JAK inhibitors described herein, or in combination with other JAK inhibitors, such as those reported in U.S. Ser. No. 11/637,545, which is incorporated herein by reference in its entirety, can be used to treat inflammation-associated cancers. In some embodiments, the cancer is associated with inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is ulcerative colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the inflammation-associated cancer is colitis-associated cancer. In some embodiments, the inflammation-associated cancer is colon cancer or colorectal cancer. In some embodiments, the cancer is gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), adenocarcinoma, small intestine cancer, or rectal cancer.

JAK-associated diseases can further include those characterized by expression of: JAK2 mutants such as those having at least one mutation in the pseudo-kinase domain (*e.g.*, JAK2V617F); JAK2 mutants having at least one mutation outside of the pseudo-kinase domain; JAK1 mutants; JAK3 mutants; erythropoietin receptor (EPOR) mutants; or deregulated expression of CRLF2.

JAK-associated diseases can further include myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), and the like. In some embodiments, the myeloproliferative disorder is myelofibrosis (e.g., primary myelofibrosis (PMF) or post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MF)). In some embodiments, the myeloproliferative disorder is post-essential thrombocythemia myelofibrosis (Post-ET MF). In some embodiments, the myeloproliferative disorder is post polycythemia vera myelofibrosis (Post-PV MF).

The present invention further provides methods of treating psoriasis or other skin disorders by administration of a topical formulation containing a compound of the invention.

In some embodiments, sustained-release formulation and dosage forms described herein can be used to treat pulmonary arterial hypertension.

In some embodiments, the sustained-release formulation and dosage forms described herein can be used to treat mast cell activation syndrome.

The present invention further provides a method of treating dermatological side effects of other pharmaceuticals by administration of the sustained-release dosage form of the invention. For example, numerous pharmaceutical agents result in unwanted allergic reactions which can manifest as acneiform rash or related dermatitis. Example pharmaceutical agents that have such undesirable side effects include anti-cancer drugs such as gefitinib, cetuximab, erlotinib, and the like. The dosage form of the invention can be administered in combination with (e.g., simultaneously or sequentially) the pharmaceutical agent having the undesirable dermatological side effect.

Further JAK-associated diseases include inflammation and inflammatory diseases. Example inflammatory diseases include sarcoidosis, inflammatory diseases of the eye (*e.g.*, iritis, uveitis, scleritis, conjunctivitis, or related disease), inflammatory diseases of the respiratory tract (*e.g.*, the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lower respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis, and other inflammatory diseases. In some embodiments, the inflammation disease of the eye is blepharitis.

The sustained-release dosage forms herein can further be used to treat ischemia reperfusion injuries or a disease or condition related to an inflammatory ischemic event such as stroke or cardiac arrest. The sustained-release dosage forms described herein can further be used to treat endotoxin-driven disease state (e.g., complications after bypass surgery or chronic endotoxin states contributing to chronic cardiac failure). The sustained-release dosage forms described herein can further be used to treat anorexia, cachexia, or fatigue such as that resulting from or associated with cancer. The sustained-release dosage forms described herein can further be used to treat restenosis, sclerodermitis, or fibrosis. The sustained-release dosage forms described herein can further be used to treat conditions associated with hypoxia or astrogliosis such as, for example, diabetic retinopathy, cancer, or neurodegeneration. See, e.g., Dudley, A.C. et al. *Biochem. J.* 2005, 390(Pt 2):427-36 and Sriram, K. et al. *J. Biol. Chem.* 2004, 279(19):19936-47. Epub 2004 Mar 2, both of which are incorporated herein by reference in their entirety. The sustained-release dosage forms described herein can be used to treat Alzheimer's disease.

The sustained-release dosage forms described herein can further be used to treat other inflammatory diseases such as systemic inflammatory response syndrome (SIRS) and septic shock.

The sustained-release dosage forms described herein can further be used to treat gout and increased prostate size due to, e.g., benign prostatic hypertrophy or benign prostatic hyperplasia.

Further JAK-associated diseases include bone resorption diseases such as osteoporosis, osteoarthritis. Bone resorption can also be associated with other conditions such as hormonal imbalance and/or hormonal therapy, autoimmune disease (e.g. osseous sarcoidosis), or cancer (e.g. myeloma). The reduction of the bone resorption due to the JAK inhibitors can be about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

In some embodiments, sustained-release dosage forms described herein can further be used to treat a dry eye disorder. As used herein, "dry eye disorder" is intended to encompass the disease states summarized in a recent official report of the Dry Eye Workshop (DEWS), which defined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface." Lemp, "The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop", *The Ocular Surface*, 5(2), 75-92 April 2007, which is incorporated herein by reference in its entirety. In some embodiments, the dry eye disorder is selected from aqueous tear-deficient dry eye (ADDE) or evaporative dry eye disorder, or appropriate combinations thereof. In some embodiments, the dry eye disorder is Sjogren syndrome dry eye (SSDE). In some embodiments, the dry eye disorder is non-Sjogren syndrome dry eye (NSSDE).

In a further aspect, the present invention provides a method of treating conjunctivitis, uveitis (including chronic uveitis), chorioditis, retinitis, cyclitis, sclieritis, episcleritis, or iritis; treating inflammation or pain related to corneal transplant, LASIK (laser assisted in situ keratomileusis), photorefractive keratectomy, or LASEK (laser assisted sub-epithelial keratomileusis); inhibiting loss of visual acuity related to corneal transplant, LASIK, photorefractive keratectomy, or LASEK; or inhibiting transplant rejection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of the invention, or a pharmaceutically acceptable salt thereof.

Additionally, the sustained-release dosage forms of the invention, optionally in combination with other JAK inhibitors such as those reported in U.S. Ser. No. 11/637,545, which is incorporated herein by reference in its entirety, can be used to treat respiratory dysfunction or failure associated with viral infection, such as influenza and SARS.

As used herein, the term “individual,” “subject,” or “patient,” refers to a human, who can be fasted or un-fasted when the dosage form of the invention is administered.

As used herein the term "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms, which are, within the scope of sound medical judgment, suitable for contact humans without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio.

As used herein, the term “treating” or “treatment” refers to one or more of (1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

Combination Therapies

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, which is incorporated herein by reference in its entirety, or other agents can be used in combination with the sustained-release dosage forms described herein for treatment of JAK-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example chemotherapeutics include proteosome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include coriticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491, all of which are incorporated herein by reference in their entirety.

Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120, all of which are incorporated herein by reference in their entirety.

Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444, both of which are incorporated herein by reference in their entirety.

Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402, all of which are incorporated herein by reference in their entirety.

In some embodiments, one or more of the compounds of the invention can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, one or more JAK inhibitors of the invention can be used in combination with a chemotherapeutic in the treatment of cancer, such as multiple myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of additional pharmaceutical agents used in the treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a JAK inhibitor of the present invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone may be reversible upon treatment with a JAK inhibitor of the present invention. The agents can be combined with the present compounds in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with at least one JAK inhibitor where the dexamethasone is administered intermittently as opposed to continuously.

In some further embodiments, combinations of sustained-release dosage forms with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

In some embodiments, the additional therapeutic agent is fluocinolone acetonide (Retisert®), or rimexolone (AL-2178, Vexol, Alcon).

In some embodiments, the additional therapeutic agent is cyclosporine (Restasis®).

In some embodiments, the additional therapeutic agent is a corticosteroid. In some embodiments, the corticosteroid is triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, or flumetholone.

In some embodiments, the additional therapeutic agent is selected from Dehydrex™ (Holles Labs), Civamide (Opko), sodium hyaluronate (Vismed, Lantibio/TRB Chemedia), cyclosporine (ST-603, Sirion Therapeutics), ARG101(T) (testosterone, Argentis), AGR1012(P) (Argentis), ecabet sodium (Senju-Ista), gefarnate (Santen), 15-(s)-hydroxyeicosatetraenoic acid (15(S)-HETE), cevilemine, doxycycline (ALTY-0501, Alacrity), minocycline, iDestrin™ (NP50301, Nascent Pharmaceuticals), cyclosporine A (Nova22007, Novagali), oxytetracycline (Duramycin, MOLI1901, Lantibio), CF101 (2S,3S,4R,5R)-3,4-dihydroxy-5-[6-[(3-iodophenyl)methylamino]purin-9-yl]-N-methyl-oxolane-2-carbamyl, Can-Fite Biopharma), voclosporin (LX212 or LX214, Lux Biosciences), ARG103 (Agentis), RX-10045 (synthetic resolvin analog, Resolvyx), DYN15 (Dyanmis Therapeutics), rivoglitazone (DE011, Daiichi Sanko), TB4 (RegeneRx), OPH-01 (Ophtalmis Monaco), PCS101 (Pericor Science), REV1-31 (Evolutec), Lacritin (Senju), rebamipide (Otsuka-Novartis), OT-551 (Othera), PAI-2 (University of Pennsylvania and Temple University), pilocarpine, tacrolimus, pimecrolimus (AMS981, Novartis), loteprednol etabonate, rituximab, diquafosol tetrasodium (INS365, Inspire), KLS-0611 (Kissei Pharmaceuticals), dehydroepiandrosterone, anakinra, efalizumab, mycophenolate sodium, etanercept (Embrel®), hydroxychloroquine, NGX267 (TorreyPines Therapeutics), actemra, gemcitabine, oxaliplatin, L-asparaginase, or thalidomide.

In some embodiments, the additional therapeutic agent is an anti-angiogenic agent, cholinergic agonist, TRP-1 receptor modulator, a calcium channel blocker, a mucin secretagogue, MUC1 stimulant, a calcineurin inhibitor, a corticosteroid, a P2Y2 receptor agonist, a muscarinic receptor agonist, an mTOR inhibitor, another JAK inhibitor, Bcr-Abl kinase inhibitor, Flt-3 kinase inhibitor, RAF kinase inhibitor, and FAK kinase inhibitor such as, for example, those described in WO 2006/056399, which is incorporated herein by reference in its entirety. In some embodiments, the additional therapeutic agent is a tetracycline derivative (e.g., minocycline or doxycline). In some embodiments, the additional therapeutic agent binds to FKBP12.

In some embodiments, the additional therapeutic agent is an alkylating agent or DNA cross-linking agent; an anti-metabolite/demethylating agent (e.g., 5-flurouracil, capecitabine or azacitidine); an anti-hormone therapy (e.g., hormone receptor antagonists, SERMs, or aromotase inhibitor); a mitotic inhibitor (e.g. vincristine or paclitaxel); an topoisomerase (I or II) inhibitor (e.g. mitoxantrone and irinotecan); an apoptotic inducers (e.g. ABT-737); a nucleic acid therapy (e.g. antisense or RNAi); nuclear receptor ligands (e.g., agonists and/or antagonists: all-trans retinoic acid or bexarotene); epigenetic targeting agents such as histone deacetylase inhibitors (e.g. vorinostat), hypomethylating agents (e.g. decitabine); regulators of protein stability such as Hsp90 inhibitors, ubiquitin and/or ubiquitin like conjugating or deconjugating molecules; or an EGFR inhibitor (erlotinib).

In some embodiments, the additional therapeutic agent(s) are demulcent eye drops (also known as "artificial tears"), which include, but are not limited to, compositions containing polyvinylalcohol, hydroxypropyl methylcellulose, glycerin, polyethylene glycol (e.g. PEG400), or carboxymethyl cellulose. Artificial tears can help in the treatment of dry eye by compensating for reduced moistening and lubricating capacity of the tear film. In some embodiments, the additional therapeutic agent is a mucolytic drug, such as N-acetyl-cysteine, which can interact with the mucoproteins and, therefore, to decrease the viscosity of the tear film.

In some embodiments, the additional therapeutic agent includes an antibiotic, antiviral, antifungal, anesthetic, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin; naphthyridine; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomycin; colistimethate; bacitracin; vancomycin; tetracyclines; rifampin and its derivatives ("rifampins"); cycloserine; beta-lactams; cephalosporins; amphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; diclofenac; flurbiprofen; ketorolac; suprofen; cromolyn; lodoxamide; levocabastin; naphazoline; antazoline; pheniramine; or azalide antibiotic.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

Example 1

Sustained-Release and Immediate-Release Formulations of Ruxolitinib Phosphate

Formulation SR-2

A 25 mg sustained-release formulation of ruxolitinib phosphate was prepared according to the following protocol. The formulation components are provided in Table 1a. Percentages are by weight.

Table 1a

Component	Function	Percentage
Ruxolitinib phosphate[a]	Active ingredient	12.2
Microcryrstalline cellulose, NF	Filler	22.0
Hypromellose, USP (Methocel K15M)	Sustained release matrix former	4.0
Hypromellose, USP (Methocel K4M)	Sustained release matrix former	16.0
Lactose monohydrate, NF	Filler	42.3
Colloidal silicon dioxide, NF	Glidant	1.0
Magnesium stearate, NF	Lubricant	0.5
Stearic acid, NF	Lubricant	2.0
Total		100

[a] On a free base basis, conversion factor for phosphate salt to free base is 0.7575.

Protocol

Step 1. Add microcrystalline cellulose, ruxolitinib phosphate, lactose monohydrate, and hypromelloses to a suitable blender and mix.

Step 2. Transfer the mix from Step 1 to a suitable granulator and mix.

Step 3. Add purified water while mixing.

Step 4. Screen the wet granules from Step 3.

Step 5. Transfer the granules from Step 4 into a suitable dryer and dry until LOD is no more than 3%.

Step 6. Screen the granules from Step 5.

Step 7. Mix colloidal silicon dioxide with granules in Step 6 in a suitable blender.

Step 8. Mix stearic acid and magnesium stearate with the blend in Step 7 and continue blending.

Step 9. Compress the final blend in Step 8 on a suitable rotary tablet press.

Formulation SR-1

An alternate 25 mg sustained-release formulation of ruxolitinib phosphate has been prepared as described below. The formulation components are provided in Table 1b. Percentages are by weight.

Table 1b

Component	Function	Percentage
Ruxolitinib phosphate[a]	Active ingredient	12.2
Microcryrstalline cellulose, NF	Filler	42.3
Hypromellose, USP (Methocel K100LV)	Sustained release matrix former	10.0
Hypromellose, USP (Methocel K4M)	Sustained release matrix former	12.0
Lactose monohydrate, NF	Filler	20.0
Colloidal silicon dioxide, NF	Glidant	1.0
Magnesium stearate, NF	Lubricant	0.5
Stearic acid, NF	Lubricant	2.0
Total		100

[a] On a free base basis, conversion factor for phosphate salt to free base is 0.7575.

Protocol

Step 1. Add microcrystalline cellulose, ruxolitinib phosphate, lactose monohydrate, and hypromelloses to a suitable blender and mix.

Step 2. Transfer the mix from Step 1 to a suitable granulator and mix.

Step 3. Add purified water while mixing.

Step 4. Screen the wet granules from Step 3.

Step 5. Transfer the granules from Step 4 into a suitable dryer and dry until LOD is no more than 3%.

Step 6. Screen the granules from Step 5.

Step 7. Mix colloidal silicon dioxide with granules in Step 6 in a suitable blender.

Step 8. Mix stearic acid and magnesium stearate with the blend in Step 7 and continue blending.

Step 9. Compress the final blend in Step 8 on a suitable rotary tablet press.

Formulation C – Immediate Release

Immediate-release dosage forms of ruxolitinib phosphate can be obtained commercially in 5, 10, 15, 20, and 25 mg doses as the drug product Jakafi® (ruxolitinib phosphate (tablets)) (NDA no. N202192). The commercially available dosage forms are the same as used in the Phase 3 COMFORT-1 and COMFORT-II studies.

Example 2

Bioavailability Study of Sustained Release Formulation

A relative bioavailability study of the sustained release and immediate formulations of ruxolitinib phosphate was conducted in healthy adult volunteers. Subjects in the fasted state were given a single oral dose of immediate-release formulation (25 mg, see Example 1) or a single oral dose of sustained-release formulation (25 mg, see Example 1). Plasma concentrations of ruxolitinib were measured and are compared in Figure 1. Table 2a provides comparative pharmacokinetic (PK) data.

Table 2a*

Treatment	n	C_{max} (nM)	T_{max} (h)	C_{12h} (nM)	C_{max}/C_{12h}	$t_{1/2}$ (h)	AUC_{0-t} (nM*h)	$AUC_{0-\infty}$ (nM*h)	Cl/F (L/h)
25 mg IR	9	1100±332 1060	0.94±0.46 0.86	45.6±38. 1 32.1	40±24 33	2.8±0.72 2.7	4340±1990 3930	4350±1990 3940	22.8±10.3 20.7
25 mg SR-1	8	333±76.1 325	2.4±0.98 2.2	121±46.8 114	3.0±1.0 2.9	5.3±1.8 5.1	3110±840 3020	3180±864 3090	27.2±6,72 26.4
25 mg SR-2	8	394±126 377	2.9±1.6 2.5	104±43.2 96.5	4.7±3.1 3.9	6.1±2.1 5.8	3520±1260 3330	3740±1400 3520	24.6±9,02 23.2
P-Values from a Crossover ANOVA of Log-Transformed Data									
		<0.0001	0.0003	--	--	<0.0001	0.040	0.070	0.070
Geometric Mean Relative Bioavailability and 90% CI (Reference = IR)									
SR-1 vs. IR		30.4% 25.4-36.4%					74.7% 62.2-89.7%	76.2% 63.1-92.0%	
SR-2 vs. IR		35.2% 29.5-42.2%					82.5% 68.7-99.1%	86.7% 71.8-105%	

*PK values are provided as mean±SD and geometric mean

Description of Bioavailability Study

This study was performed to evaluate pharmacokinetic performance of two ruxolitinib phosphate sustained release (SR) formulations compared to the ruxolitinib phosphate immediate release (IR) tablets. The study was conducted as a 3-period study in which each subject received the IR tablets, the SR-1 tablets and the SR-2 tablets, all in fasted state. All treatments were administered as a single dose in one tablet. Nine healthy subjects enrolled in this study received IR tablets in Period 1, and 8 subjects continued on the study were randomized into 2 sequences to receive SR-1 and SR-2 tablets in Period 2 and Period 3.

The 9 subjects enrolled in the study received a single dose of IR tablets, SR-1 tablets and SR-2 tablets, according to the randomization schedule (see Table 2b). Dosing was administered orally after at least 10 hour overnight fast, and a standardized meal was served

approximately 3 hours after administration. A washout period of 7 days (not less than 5 days) was instituted between the treatment periods.

Blood samples for determination of plasma concentrations of ruxolitinib were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 and 36 hours post-dose using lavender top (K2EDTA) Vacutainer® tubes. No samples were collected for determination of urine concentrations of ruxolitinib.

Table 2b. Randomization Schedule for Study

Sequence	Period 1	Period 2	Period 3	Subject
1	25 mg IR tablet fasted	25 mg SR-1 tablet fasted	25 mg SR-2 tablet fasted	102*, 103, 106, 107, 109
2	25 mg IR tablet fasted	25 mg SR-2 tablet fasted	25 mg SR-1 tablet fasted	101, 104, 105, 108

*Subject withdrew from the study before the start of Period 2

Plasma and urine samples were shipped to Incyte Corporation for determination of ruxolitinib concentrations. The plasma samples were assayed by validated, GLP, LC/MS/MS methods with a linear range of 1 to 1000 nM.

All PK blood samples were collected within 5 minutes of their scheduled time, and therefore the schedule times relative to the time of dose administration were used for all pharmacokinetic analyses.

Standard non-compartmental pharmacokinetic methods were used to analyze the ruxolitinib plasma concentration data using Phoenix WinNonlin version 6.0 (Pharsight Corporation, Mountain View, CA). Thus, C_{max} and T_{max} were taken directly from the observed plasma concentration data. The absorption lag time (T_{lag}) was defined as the sampling time immediately preceding that corresponding to the first measurable (non-zero) concentration. The terminal-phase disposition rate constant (λ_z) was estimated using a log-linear regression of the concentration data in the terminal disposition phase, and $t_{1/2}$ was estimated as $\ln(2)/\lambda_z$. AUC_{0-t} was estimated using the linear trapezoidal rule for increasing concentrations and the log-trapezoidal rule for decreasing concentrations, and the total $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/\lambda_z$. The oral-dose clearance (Cl/F) was estimated as $Dose/AUC_{0-\infty}$, and the terminal-phase volume of distribution (V_z/F) was estimated as $Dose/[AUC_{0-\infty}*\lambda_z]$.

The log-transformed pharmacokinetic parameters were compared among the treatments using a 2-factor ANOVA with the fixed factor for treatment and random factor for

subject. The relative bioavailability of the fasted administration of the SR formulations (test treatments) compared to fasted administration of the IR tablets (reference treatment) were estimated using the geometric mean relative bioavailability and 90% confidence intervals for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, which were calculated from the adjusted means (least square means) from the ANOVA. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Example 3

Sustained-Release Clinical Trial

A Phase 2 clinical trial was carried out in patients with myelofibrosis (MF). A total of 41 subjects were enrolled, and spleen volume and total symptom scores were obtained at baseline. Tablets of sustained-release formulation SR-2 (see Example 1) were administered to fasted patients. All patients were treated with 25 mg once daily doses for 8 weeks. After 8 weeks, depending upon the clinical response, the investigator was allowed to (a) maintain the same dose of SR-2, (b) increase the dose to 50 mg once daily, (c) increase the dose to alternating doses of 25 mg and 50 mg, dosed once daily, or (d) switch to treatment with the immediate release formulation.

Data related to spleen volume and total symptom scores are provided in Figures 2 and 3 together with comparative data from the COMFORT-1 Study where patients were dosed only with the immediate-release formulation. See Example A below for details of the COMFORT-1 Study. As can be seen in Figures 2 and 3, treatment with the 25 mg sustained-release formulation was nearly as effective as the immediate-release formulation in the COMFORT-I study. Percentages of spleen volume responders in COMFORT-1 as shown in Figure 2 were 39.4% and 43.9% at 12 weeks and 24 weeks, respectively. The percentage of spleen volume responders in the sustained-release study at week 16 was 28.9%. Similarly, the percentages of total symptom score responders in COMFORT-1 as shown in Figure 3 were 46.3% and 45.9% at 12 weeks and 24 weeks, respectively. The percentage of total symptom score responders in the sustained release study as shown in Figure 3 was 36.8%.

Data relating to mean platelet count and mean hemoglobin levels (Hgb) is presented below in Table 3 together with comparative data from the COMFORT-I study. As can be seen from the data, the mean change from baseline platelet count in the SR patients was about half of what was observed in COMFORT-I. Similar results are seen for hemoglobin levels. Data is shown as mean±SD.

Table 3

Parameter	Sustained-Release Study	COMFORT-I Study (active)	COMPFORT-I Study (placebo)
N	41	155	154
Mean Baseline platelet count, $x10^9$/L	274 ± 193	321 ± 202	280 ± 152
Mean Baseline Hgb in patient with no transfusions, g/L	105 ± 17	108 ± 20	106 ± 22
	Week 16	**Week 12**	**Week 12**
Mean total daily dose, mg	34	30.4	0
Mean change from baseline platelet count, $x10^9$/L	-65 ± 101	-131 ± 143	-9 ± 75
Mean change from baseline Hgb, g/L	-7.4 ± 13.3	-13.2 ± 15.5	0.3 ± 11.5

Example 4

Comparison of Steady State Plasma Concentrations of Ruxolitinib between SR and IR Formulations in MF Patients

Steady state plasma concentrations of ruxolitinib in myelofibrosis (MF) patients receiving repeating 25 mg doses are compared in Figure 4 between sustained release (SR) and immediate release (IR) formulations. Comparative pharmacokinetic parameters are provided below in Table 4a.

Table 4a*

Formula and Regimen	n	C_{max} (nM)	T_{max} (h)	C_{min} (nM)	$t_{1/2}$ (h)	$AUC_{0-\tau}$ (nM*h)	AUC_{0-t} (nM*h)	Cl/F (L/h)
SR 25 mg QD[a]	39	397±175 368	2.35±1.75 1.88	32±40.6 --	7.33±3.73 6.42	3650±2450 3020	2060±1140 1810	32.0±18.0 27.1
IR 25 mg BID[b] (1A)	27	1481±575 1374	0.83±0.45 0.74	47±54 --	1.94±0.50 1.88	4363±2066 3949	4148±1885 3778	22.7 ±10.1 20.7
IR 25 mg QD[b] (2A)	6	1417±150 1410	0.84±0.38 0.78	0±0 --	1.60±0.36 1.57	3567±777 3494	3291±604 3243	23.9±5.5 23.4
IR 25 mg BID[b] (2C)	7	1650±506 1578	0.79±0.49 0.68	85±102 43	1.96±0.59 1.90	4939±2566 4463	4444±1918 4120	19.9±8.1 18.3
SR 25 mg single dose[c]	8	394±126 377	2.9±1.6 2.5	--	6.1±2.1 5.8	3740±1400 3520	--	24.6±9.02 23.2

[a]From SR study described in Example 3
[b]From IR study described below (Description of Open-Label Study in MF patients)
[c]From single dose study described in Example 2 ($AUC_{0-\tau}$ will be $AUC_{0-\infty}$)
*Values are mean±SD and geometric mean.

Description of Open-Label Study in MF patients

General Description

This was an open-label study exploring the safety, tolerability, and efficacy of ruxolitinib, administered orally to patients with primary myelofibrosis (PMF) and post polycythemia vera/essential thrombocythemia myelofibrosis (Post-PV/ET MF). The study was comprised of 3 parts: Part 1-dose escalation and expansion, bid dosing, Part 2-alternative dosing schedules (A, B and C), and Part 3-three independent patient groups (Group I, II and III). Eight dose regimens were evaluated in 3 parts. The Part 1 evaluated two dose levels of 25 mg bid and 50 mg bid, Part 2 studied five dose regimens of 10 mg bid, 25 mg bid, 25 mg qd, 50 mg qd and 100 mg qd and Part 3 assessed six dose regimens of 10 mg bid, 15 mg bid, 25 mg bid, 50 mg qd, 100 mg qd and 200 mg qd. A total of 154 subjects were enrolled; 32 subjects enrolled in Part 1, 29 subjects in Part 2 and 93 subjects in Part 3. See Table 4b (qd = once per day; bid = twice per day).

In Part 1, the pharmacokinetic blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 4, 6 and 9 hours post-dose on Days 1 and 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 2 and 3, using lavender top (K3EDTA) Vacutainer® tubes. In Part 2, the pharmacokinetic samples were collected at pre-dose and 0.5, 1, 1.5, 2, 4, 6 and 9 hours post-dose on Day 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 2 and 3. In Part 3, the pharmacokinetic samples were collected at pre-dose and 2 hours after administration of the morning dose of ruxolitinib on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3.

Plasma concentration data from Cycle 1 for subjects in Part 1 and 2 were used for non-compartmental analysis while all plasma concentration data were used for population PK analysis.

Following fasting, oral, first-dose or multiple-dose administration of ruxolitinib phosphate tablets, the drug was absorbed rapidly, typically attaining peak plasma concentrations within 0.3 to 2 hours after administration in all subjects. Plasma concentrations subsequently declined in a monophasic or biphasic fashion.

The mean C_{max} and AUC increased approximately linearly proportional to dose from 10 mg to 100 mg. The pharmacokinetics of ruxolitinib in MF patients was similar to that in healthy volunteers.

Detailed Description of Clinical Trial

This multicenter, open-label, non-randomized, dose escalation clinical study was conducted by M.D. Anderson Cancer Center, Houston, TX and Mayo Clinic, Rochester, MN, according to Protocol INCB 18424-251, and 154 patients with PMF or Post-PV/ET MF were enrolled and received at least a single dose according to the study plan in Table 4b. The study was comprised of 3 parts: Part 1-dose escalation and expansion cohort, bid dosing, Part 2- alternative dosing schedules (A, B and C), and Part 3-three independent patient groups (Group I, II and III). Schedules A, B and C in Part 2 were once daily (qd) dosing regimens, low dose regimen of 10 mg bid and induction/maintenance regimen, respectively. Part 3 was studied in three separate groups of patients to further evaluate the safety and efficacy of selected starting dose levels and to explore dose modification on an individual patient basis as appropriate. Dose hold and withdrawal for safety were defined in terms of platelet count and absolute neutrophil count (ANC) while provision for dose increase was provided based on inadequate efficacy defined by change in spleen size.

Ruxolitinib phosphate tablets (5 and 25 mg) were administered as oral doses with water in an outpatient setting. Doses ranged from 10 mg bid to 50 mg bid, and from 25 mg qd to
200 mg qd. The individual patient participation was expected to be approximately 12-24 months; patients might continue on therapy indefinitely if they did not meet any of the withdrawal criteria, did not have disease progression and are receiving some clinical benefit.

In Part 1, the pharmacokinetic blood samples were collected at pre-dose and 0.5, 1, 1.5, 2,
4, 6 and 9 hours post-dose on Days 1 and 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 2 and 3, using lavender top (K3EDTA) Vacutainer® tubes. In Part 2, the pharmacokinetic samples were collected at pre-dose and 0.5, 1, 1.5, 2, 4, 6 and 9 hours post-dose on Day 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 2 and 3. In Part 3, the pharmacokinetic samples were collected at pre-dose and 2 hours after administration of the morning dose on Day 15 of Cycle 1 and Day 1 of Cycles 2 and 3.

Table 4b

Part	Schedule	Dose Regimen
1	A	25 mg bid

1	B	50 mg bid
2	A	25 mg qd
2	A	50 mg qd
2	A	100 mg qd
2	B	10 mg bid
2	C	25 mg bid
3	I	50 mg qd
3	I	10 mg qd
3	I	25 mg bid
3	II	100 mg qd
3	II	200 mg qd
3	III	10 mg bid
3	III	15 mg bid

Plasma samples were shipped to Incyte Corporation and assayed by a validated, GLP, LC/MS/MS method with a linear range of 1 to 1000 nM and a limit of quantification of 1 nM.

Generally, the actual time post-dose was used for pharmacokinetic analyses. However, the dose information on Cycle 1 Day 15 for patients in Part 2 and three additional patients in Part 1 were not collected. The nominal time were used for pharmacokinetic analyses for these patients. The dose information on Cycle 1 Day 15 for four additional patients was questionable. Hence, the nominal time were used for these patients also. Plasma concentrations at 12 hours post dose for bid or 24 hours post dose for qd on Cycle 1, Day 15 were imputed by sample at pre-dose on Cycle 1 Day 15 to calculate steady state $AUC_{0-\tau}$.

Standard noncompartmental pharmacokinetic methods were used to analyze the ruxolitinib plasma concentration data using WinNonlin version 6.0 (Pharsight Corporation, Mountain View, CA). Thus, C_{max} and T_{max} were taken directly from the observed plasma concentration data. For single dose, the terminal-phase disposition rate constant (λ_z) was estimated using a log-linear regression of the concentration data in the terminal disposition phase, and $t_{1/2}$ was estimated as $\ln(2)/\lambda_z$. AUC_{0-t} was estimated using the linear-trapezoidal rule for increasing concentrations and the log-trapezoidal rule for decreasing concentrations, and the total $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/\lambda_z$. The oral-dose clearance (Cl/F) was estimated as Dose/ $AUC_{0-\infty}$, and the terminal-phase

volume of distribution (V_z/F) was estimated as Dose/[$AUC_{0-\infty}$ *λ_z].

For the multiple-dose data, λ_z was estimated using a log-linear regression of the concentration data in the terminal disposition phase, and $t_{1/2}$ was estimated as ln(2)/ λ_z. The AUC over one dosing interval (AUC_{0-12h} for q12h administration, or AUC_{0-24h} for q24h administration) was estimated using the linear trapezoidal rule for increasing concentrations and the log-trapezoidal rule for decreasing concentrations. The Cl/F was estimated as Dose/AUC, and V_z/F was estimated as Dose/[AUC* λ_z]. Additionally, the C_{min} and AUC_{0-t} (Area under the steady-state plasma concentration-time curve from time zero to the time of the last sample obtained) were calculated for the multiple-dose data.

The PK parameters of ruxolitinib were summarized for each dose group using descriptive statistics, and the log-transformed ruxolitinib PK parameters were compared among the dose groups using a 1-factor analysis of variance. The dose-proportionality of C_{max} and AUC was evaluated using a power function regression model (eg, $C_{max} = \alpha \cdot Dose\beta$).

The pharmacokinetics of ruxolitinib in MF patients was similar to that in healthy volunteers.

Example 5

Comparative Efficacy of Sustained Release and Immediate Release Formulations

Enlarged spleen is a common and prominent symptom of myelofibrosis. Reduction in spleen volume serves as a measure for assessing the effectiveness of a given treatment. Table 5a reports the mean reduction in spleen volume in MF patients enrolled in the sustained-release study (See Example 3) at 16 weeks of treatment, while Table 5b reports the mean reduction in spleen volume in MF patients enrolled in the COMFORT-I study (immediate release, see Comparative Example A) at 24 weeks of treatment. As can be seen from the data, both the sustained-release and immediate release treatment regimens were effective in reducing spleen volume.

Table 5a
Spleen Volume (cm^3) from Sustained-Release Study

	Percent Change from Baseline to Week 16 (%)
n	40

Mean	-22.3
STD	20.79
Median	-21.7
(MIN,MAX)	(-64.6,43.6)

Table 5b
Spleen Volume (cm^3) from COMFORT I (Immediate-Release)

Percent Change from Baseline	Treatment Group			
	To Week 12 (%)		To Week 24 (%)	
	Ruxolitinib (N=155)	Placebo (N=154)	Ruxolitinib (N=155)	Placebo (N=154)
n	148	132	139	106
Mean	-32.0	8.4	-31.6	8.1
STD	15.58	14.61	18.92	15.31
Min	-74.4	-26.2	-75.9	-46.4
Median	-31.7	6.1	-33.0	8.5
Max	3.8	64.6	25.1	48.8

Effectiveness of a treatment regimen in an MF patient can also be assessed by Total Symptom Score. In calculating Total Symptom Score, symptoms of MF were assessed using a symptom diary (modified MFSAF v2.0 diary) where subjects recorded answers to queries regarding MF symptoms on a handheld device. Symptoms assessed included filling up quickly/early satiety, abdominal discomfort, abdominal pain, inactivity, night sweats, itching, and bone/muscle pain.

Table 5c reports the Total Symptom Score results in the sustained-release study (see Example 3) while Table 5d reports the Total Symptom Score results in the COMFORT-I

study (immediate-release, see Comparative Example A) at 24 weeks. As can be seen from the data, both the SR and IR regimens were effective at treating MF in patients.

Table 5c
Total Symptom Scores from Sustained-Release Study

	Percent Change from Baseline to Week 16
n	38
Mean	-50.4
STD	31.16
Median	-48.6
(MIN,MAX)	(-100.0,12.7)

Table 5d
Total Symptom Score from COMFORT I Study (Immediate-Release)

	Treatment Group			
Percent Change from Baseline	Ruxolitinib To Week 16 (N=155)	Placebo To Week 16 (N=154)	Ruxolitinib To Week 24 (N=155)	Placebo To Week 24 (N=154)
n	140	124	129	103
Mean	-40.5	37.8	-46.1	41.8
STD	54.31	93.92	48.55	99.26
Min	-100.0	-82.5	-100.0	-100.0
Median	-51.1	12.7	-56.2	14.6
Max	292.5	464.8	108.3	511.6

Example 6

Comparison of Adverse Events in Patients Enrolled in the Sustained-Release Study and COMFORT-I (Immediate-Release) Study

Data for adverse events relating to anemia, thrombocytopenia, neutropenia, and all Grade 3 or higher adverse events are compared for the sustained–release and COMFORT-I (immediate-release) studies (see Example 3 and Comparative Example A for descriptions of the studies) in Table 6a. Adverse events are graded according to CTCAE criteria which can be found online at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm or evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. A Grade 3 adverse event generally corresponds to a reaction that is severe or medically significant, but not immediately life-threatening where hospitalization or prolongation of hospitalization is indicated and where the reaction is disabling to the extent of limiting self care. Higher Grades are 4 (life-threatening requiring urgent intervention) and 5 (death). For anemia, Grade 3 corresponds to Hgb<8.0 g/dL; <4.9 mmol/L; <80 g/L, where a transfusion is indicated. For thrombocytopenia (decreased platelet count), Grade 3 corresponds to <50,000-25,000/mm^3; <50.0-25.0x10^9 /L. The sustained-release data was evaluated for patients over the course of 16 weeks. Mean duration of exposure to ruxolitinib in the COMFORT-I was approximately 242 days. Typically, the majority of hematologic adverse events occur within the first few months of therapy as observed in the COMFORT-I study.

As can be seen from the data in Table 6a, adverse events relating to anemia, thrombocytopenia, neutropenia, and all events that were considered Grade 3 or higher occurred less frequently in the sustained-release study compared with the COMFORT-I immediate-release study.

Table 6a
Percent of Patients with Selected Grade 3 or Higher Adverse Events

Adverse Event	SR Study	COMFORT I Ruxolitinib	COMFORT I Placebo
All ≥Grade 3 Adverse Events	17.1%	47.1%	44.4%
Anemia	0%	15.5%	4.6%
Thrombocytopenia	2.4%	8.4%	2.0%
Neutropenia	0%	1.3%	0.7%

The occurrence of blood-related adverse events are further compared in Tables 6b and 6c which report the number and percentage of patients in the studies exhibiting certain reactions including anemia and thrombocytopenia. The sustained-release data was evaluated

for patients over the course of 16 weeks. Mean duration of exposure to ruxolitinib in the COMFORT-I study was approximately 242 days. The vast majority of hematologic adverse events occur within the first few months of therapy as observed in the COMFORT-I study. As can be seen from the data in the tables, the number and percentage of patients exhibiting blood-related adverse events is lower in the sustained-release study. Additionally, the severity of the adverse events is lesser in the sustained–release study.

Table 6b
Treatment-Related Haematologic Adverse Events By Organ Class, Preferred Term, and Maximum Severity in the Sustained–Release Study (First 16 Weeks)*

MedDRA System Organ Class/ MedDRA Preferred Term	Ruxolitinib (N=41) Mi	Mo	Se	LT	Any
Number (%) of Subjects With Any Adverse Events	16	9	7	0	32 (78.0)
Blood and lymphatic system disorders	3	4	1	0	8 (19.5)
Anaemia	0	2	0	0	2 (4.9)
Thrombocytopenia	3	2	1	0	6 (14.6)

*Mi (mild), Mo (moderate), Se (severe), LT (life threatening)

Table 6c
Treatment-Related Adverse Events By MedDRA System Organ Class, Preferred Term, and Maximum Severity in COMFORT I*

MedDRA System Organ Class/ MedDRA Preferred Term	Ruxolitinib (N=155) Mi	Mo	Se	LT	FT	Any	Placebo (N=151) Mi	Mo	Se	LT	FT	Any
Number (%) of Subjects With Any Adverse Events (98.0)	20	58	55	9	9	151 (97.4)	23	58	53	4	10	148
Blood and lymphatic												

system disorders (37.1)	20	28	27	10	0	85 (54.8)	18	21	15	2	0	56
Anaemia (13.9)	4	20	16	8	0	48 (31.0)	4	10	7	0	0	21
Thrombocytopenia 9.3)	21	19	11	2	0	53 (34.2)	6	5	2	1	0	14 (

*Mi (mild), Mo (moderate), Se (severe), LT (life threatening), FT (fatal)

Comparative Example A

COMFORT I Clinical Trial – Immediate Release Formulation

A Phase 3 clinical trial was completed showing efficacy of ruxolitinib in myelofibrosis patients. In this double-blind trial, patients with intermediate-2 or high risk myelofibrosis were randomly assigned to twice-daily oral, immediate-release (see Example 1) ruxolitinib (155 patients) or placebo (154 patients). The starting dose of ruxolitinib depended on the baseline platelet count: 15 mg twice daily for a platelet count of 100×109 to 200×109 per liter and 20 mg twice daily for a count that exceeded 200×109 per liter. The dose was adjusted for lack of efficacy or excess toxicity. The primary end point was the proportion of patients with a reduction in spleen volume of 35% or more at 24 weeks, assessed by means of magnetic resonance imaging. Secondary end points included the durability of response, changes in symptom burden (assessed by the total symptom score), and overall survival.

The proportion of patients with a reduction of 35% or more in spleen volume at week 24 (primary end point) was 41.9% in the ruxolitinib group as compared with 0.7% in the placebo group. The proportion of patients with a reduction of 50% or more in the total symptom score from baseline to week 24, a pre-specified secondary end point, was significantly higher in the ruxolitinib group than in the placebo group (45.9% vs. 5.3%; odds ratio, 15.3; 95% CI, 6.9 to 33.7; P<0.001).

The study showed that ruxolitinib was associated with reductions in splenomegaly and symptoms that are prominent manifestations of myelofibrosis and appeared to be associated with an improvement in overall survival. Additionally, the most common toxic effects of anemia and thrombocytopenia were generally managed with dose modification. Details regarding this study are provided in Verstovsek, S., et al. "A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis," N. Eng. J. Med., 2012, Mar 1:366(9):799-807, which is incorporated herein by reference in its entirety.

Comparative Example B

COMFORT II Clinical Trial – Immediate Release Formulation

A Phase 3 clinical trial was completed showing the superiority of ruxolitinib treatment in myelofibrosis patients compared with best available therapy. Continuous ruxolitinib therapy, as compared with the best available therapy, was associated with marked and durable reductions in splenomegaly and disease-related symptoms, improvements in role functioning and quality of life, and modest toxic effects.

Myelofibrosis patients were randomly assigned, in a 2:1 ratio, to receive ruxolitinib or the best available therapy, which included any commercially available agents (as monotherapy or in combination) or no therapy at all and which could be changed during the treatment phase. The starting dose of ruxolitinib tablets was 15 mg twice daily of an immediate release formulation (See Example 1) if the baseline platelet count was 200×109 per liter or less and 20 mg orally twice daily if the baseline platelet count was greater than 200×109 per liter.

The primary end point was a reduction of 35% or more in spleen volume from baseline at week 48. At week 48, most of the patients in the ruxolitinib group had a reduction in spleen volume. Only patients in the ruxolitinib group met the criterion for the primary end point,

at least a 35% reduction in spleen volume from baseline at 48 weeks (28%, vs. 0% in the group receiving the best available therapy; $P<0.001$). Patients in the ruxolitinib group, as compared with patients receiving the best available therapy, had improved quality of life and role functioning. At week 48, patients receiving ruxolitinib had marked reductions in myelofibrosis associated symptoms, including appetite loss, dyspnea, fatigue, insomnia, and pain, whereas patients receiving the best available therapy had worsening symptoms.

Thrombocytopenia and anemia occurred more frequently in the patients receiving ruxolitinib than in those receiving the best available therapy, but these events were generally manageable with dose modifications, transfusions of packed red cells, or both. Additional details of the study are provided in Harrison, C. et al., "JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis," N. Eng. J. Med., 2012, Mar 1;366(9):787-98 which is incorporated herein by reference in its entirety.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all

patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A sustained-release dosage form comprising at least one active ingredient which is ruxolitinib, or a pharmaceutically acceptable salt thereof, wherein said ruxolitinib, or pharmaceutically acceptable salt thereof, is present in said dosage form in an amount of about 10 to about 60 mg on a free base basis.

2. The sustained-release dosage form of claim 1 wherein said ruxolitinib, or pharmaceutically acceptable salt thereof, is present in said dosage form in an amount of about 25 mg on a free base basis.

3. The sustained-release dosage form of claim 1 or 2, wherein said active ingredient is ruxolitinib phosphate.

4. The sustained-release dosage form of any one of claims 1 to 3, wherein administration of said dosage form to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 700 nM or less.

5. The sustained-release dosage form of any one of claims 1 to 3, wherein administration of said dosage form to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 200 to about 700 nM.

6. The sustained-release dosage form of any one of claims 1 to 3, wherein administration of said dosage form to a human results in a mean peak plasma concentration (C_{max}) of ruxolitinib of about 300 to about 400 nM.

7. The sustained-release dosage form of any one of claims 1 to 6, wherein administration of said dosage form to a human state results in a mean time to peak plasma concentration (T_{max}) of ruxolitinib of about 1.5 hours or more.

8. The sustained-release dosage form of any one of claims 1 to 6, wherein administration of said dosage form to a human results in a mean time to peak plasma concentration (T_{max}) of ruxolitinib of about 1.5 hours to about 5 hours.

9. The sustained-release dosage form of any one of claims 1 to 8, wherein administration of said dosage form to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 10 or less.

10. The sustained-release dosage form of any one of claims 1 to 8, wherein administration of said dosage form to a human results in a ratio of mean peak plasma concentration (C_{max}) to mean 12-hour plasma concentration (C_{12h}) of ruxolitinib of about 4 or less.

11. The sustained-release dosage form of any one of claims 1 to 10, wherein administration of said dosage form to a human results in a mean half-life ($t_{1/2}$) of from about 3.5 hours to about 11 hours.

12. The sustained-release dosage form of any one of claims 1 to 10, wherein administration of said dosage form to a human results in a mean half-life ($t_{1/2}$) of from about 4 hours to about 8 hours.

13. The sustained-release dosage form of any one of claims 1 to 12, wherein administration of a single dose of said dosage form to a human results in mean bioavailability ($AUC_{0-\infty}$) of ruxolitinib of about 3000 to about 4000 nM*h.

14. The sustained-release dosage form of any one of claims 1 to 12, wherein administration of a single dose of said dosage form to a human results in mean bioavailability ($AUC_{0-\infty}$) of ruxolitinib of about 3100 to about 3800 nM*h.

15. The sustained-release dosage form of any one of claims 1 to 12 comprising one or more cellulosic ethers.

16. The sustained-release dosage form of claim 15 comprising hydroxypropyl methylcellulose.

17. The sustained-release dosage form of claim 15 comprising from about 10% to about 30% by weight of hydroxypropyl methylcellulose.

18. The sustained-release dosage form of any one of claims 1 to 17 which is in the form of a tablet or capsule.

19. The sustained-release dosage form of any one of claims 1 to 18, comprising 25 mg of ruxolitinib on a free base basis, or a pharmaceutically acceptable salt thereof, wherein administration to a patient results in a mean ruxolitinib plasma level of about 75 to about 500 nM for at least about 8 hours.

20. The sustained-release dosage form of claim 19 comprising 12-13% ruxolitinib phosphate by weight on a free base basis and 19-23% by weight of one or more hypromelloses.

21. The sustained-release dosage form of claim 19 comprising 12.2% ruxolitinib phosphate by weight on a free base basis and 20% by weight or 22% by weight of one or more hypromelloses.

22. The sustained-release dosage form of any one of claims 19 to 21, wherein administration to a patient results in a ruxolitinib plasma level of about 75 to about 500 nM for at least about 8 hours.

23. The sustained-release dosage form of any one of claims 19 to 21, wherein administration to a patient results in a ruxolitinib plasma level of about 75 to about 500 nM for at least about 12 hours.

24. The sustained-release dosage form of any one of claims 1 to 23 comprising 25 mg ruxolitinib phosphate on a free base basis, wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean base platelet count of no more than about 100 x 10^9/L.

25. The sustained-release dosage form of claim 24 wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean base platelet count of no more than about 80 x 10^9/L.

26. The sustained-release dosage form of claim 24 wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean base platelet count of no more than about 60 x 10^9/L.

27. The sustained-release dosage form of claim 24 wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean base platelet count of no more than about 40 x 10^9/L.

28. The sustained-release dosage form of any one of claims 1 to 27, comprising 25 mg ruxolitinib phosphate on a free base basis, wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean hemoglobin of no more than about 15 g/L.

29. The sustained-release dosage form of claim 28 wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean hemoglobin of no more than about 10 g/L.

30. The sustained-release dosage form of claim 28 wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean hemoglobin of no more than about 8 g/L.

31. The sustained-release dosage form of claim 28 wherein administration of said dosage form to a patient for at least 16 weeks results in a mean decrease in mean hemoglobin of no more than about 6 g/L.

32. The sustained-release dosage form of any one of claims 1 to 31, comprising (1) ruxolitinib phosphate, or a pharmaceutically acceptable salt thereof, (2) microcrystalline cellulose, (3) hypromellose, (4) lactose monohydrate, (5) colloidal silicon dioxide, (6) magnesium stearate, and (7) stearic acid.

33. A method of treating a disease associated with JAK activity in a patient in need thereof, comprising administering the dosage form of any one of claims 1 to 32 to said patient, wherein said disease is selected from an autoimmune disease, a skin disorder, allograft rejection, graft versus host disease, multiple sclerosis, rheumatoid arthritis, juvenile

arthritis, type I diabetes, lupus, inflammatory bowel disease, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, autoimmune thyroid disorder, a viral disease, Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV), Human Papilloma Virus (HPV), cancer, a myeloproliferative disorder, an inflammatory disease, an inflammatory disease of the eye, iritis, uveitis, scleritis, conjunctivitis, an inflammatory disease of the respiratory tract, an inflammatory disease of the upper respiratory tract, an inflammatory disease of the lower respiratory tract, an inflammatory myopathy, myocarditis, ischemia reperfusion or a disorder related to an ischemic event, anorexia or cachexia resulting from or associated with cancer, fatigue resulting from or associated with cancer, a bone resorption disease, or mast cell activation syndrome.

34. The method of claim 33, wherein said autoimmune disease is bullous skin disorder.

35. The method of claim 34, wherein said bullous skin disorder is pemphigus vulgaris (PV) or bullous pemphigoid (BP).

36. The method of claim 33, wherein said skin disorder is atopic dermatitis, psoriasis, skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.

37. The method of claim 36, wherein said skin disorder is psoriasis.

38. The method of claim 33, wherein said myeloproliferative disorder (MPD) is polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post PV-MF), post-essential thrombocythemia myelofibrosis (post ET-MF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), or systemic mast cell disease (SMCD).

39. The method of claim 38, wherein said disease is primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post PV-MF), post-essential thrombocythemia myelofibrosis (post ET-MF), polycythemia vera (PV), or essential thrombocythemia (ET).

40. The method of claim 38, wherein said disease is primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post PV-MF), or post-essential thrombocythemia myelofibrosis (post ET-MF).

41. The method of claim 33, wherein said cancer is a solid tumor, myeloma, prostate cancer, renal cancer, hepatic cancer, breast cancer, lung cancer, thyroid cancer, Kaposi's sarcoma, Castleman's disease, pancreatic cancer, hematological cancer, lymphoma, leukemia, multiple myeloma, skin cancer, cutaneous T-cell lymphoma or cutaneous B-cell lymphoma.

42. The method of claim 33, wherein said bone resorption disease is osteoporosis, osteoarthritis, bone resorption associated with hormonal imbalance, bone resorption associated with hormonal therapy, bone resorption associated with autoimmune disease, or bone resorption associated with cancer.

43. The method of claim 33, wherein said oral dosage form is administered once daily.