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(54) **NOVEL FORMULATIONS OF A BRUTON'S TYROSINE KINASE INHIBITOR**

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(57)

ABSTRACT

Described herein is the Bruton's tyrosine kinase (Btk) inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, including novel pharmaceutical formulations thereof. Also disclosed are pharmaceutical compositions that include the Btk inhibitor, as well as methods of using the Btk inhibitor, alone or in combination with other therapeutic agents, for the treatment of autoimmune diseases or conditions, heteroimmune diseases or conditions, cancer, including lymphoma, and inflammatory diseases or conditions.

FIG. 1

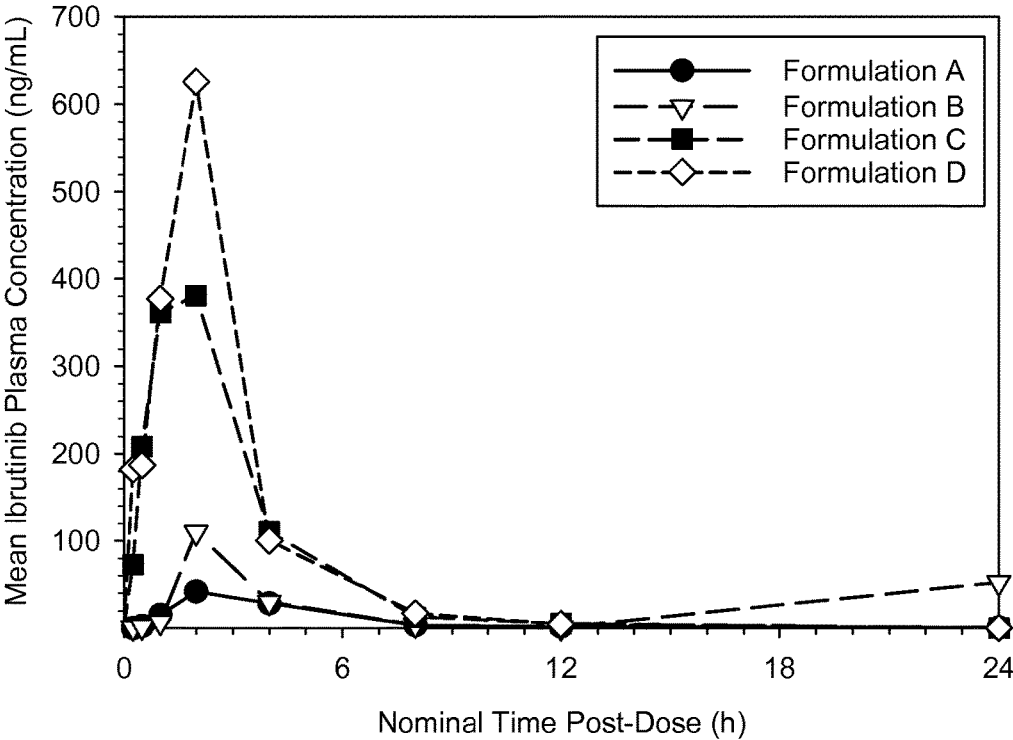


FIG. 2

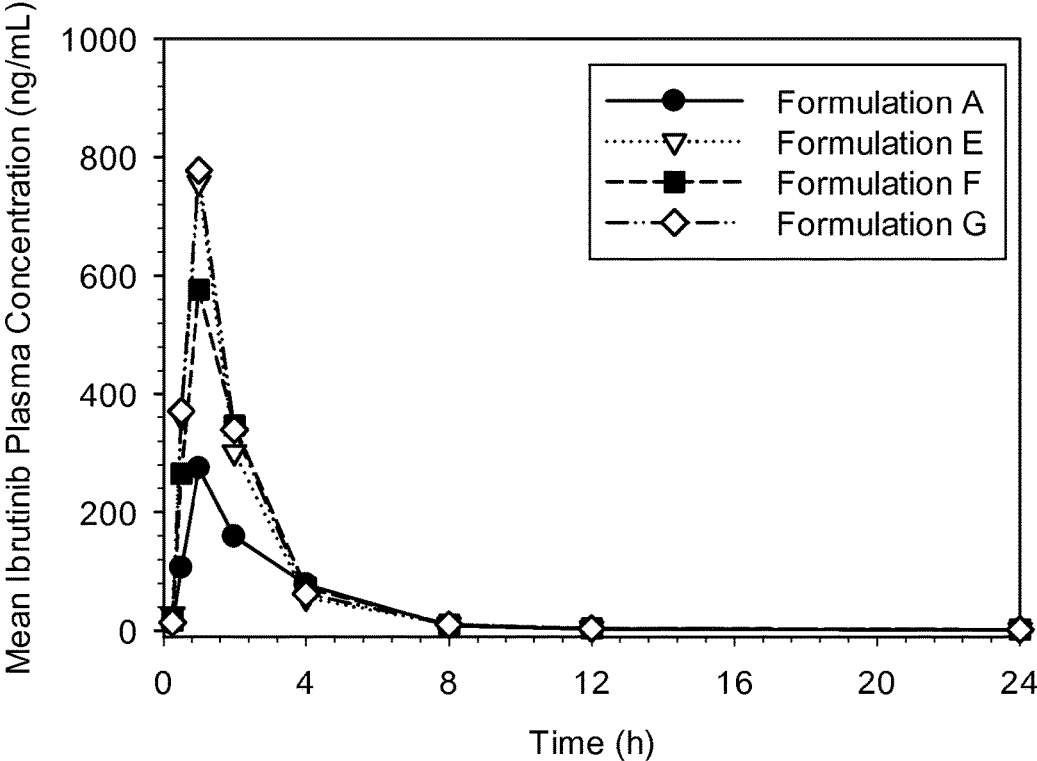


FIG 3.

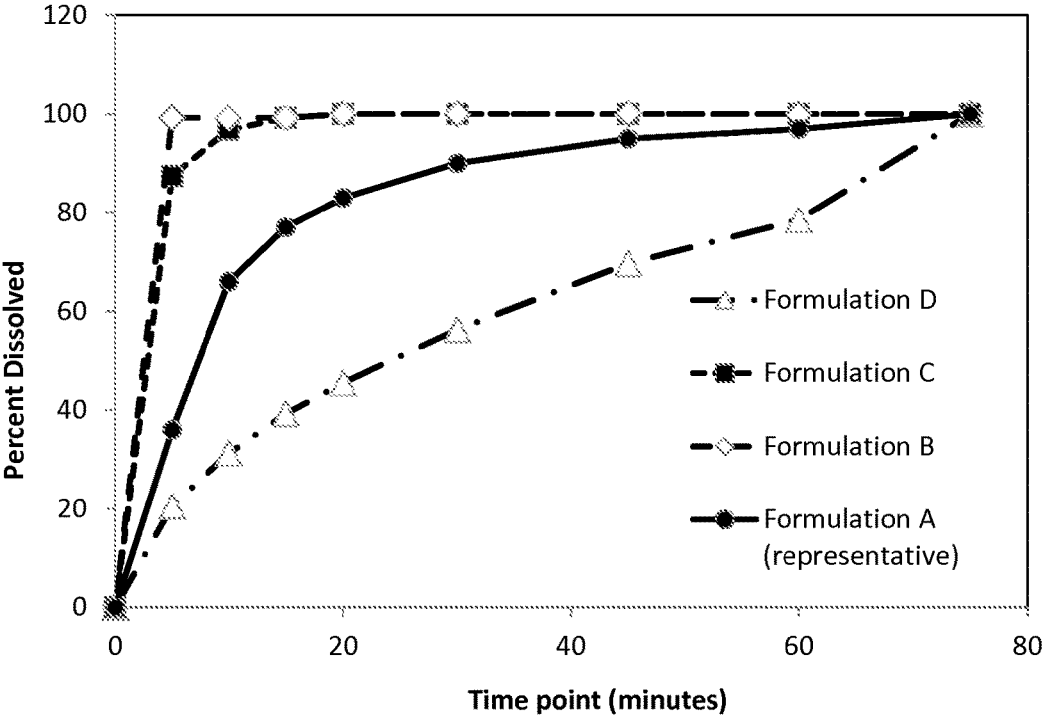
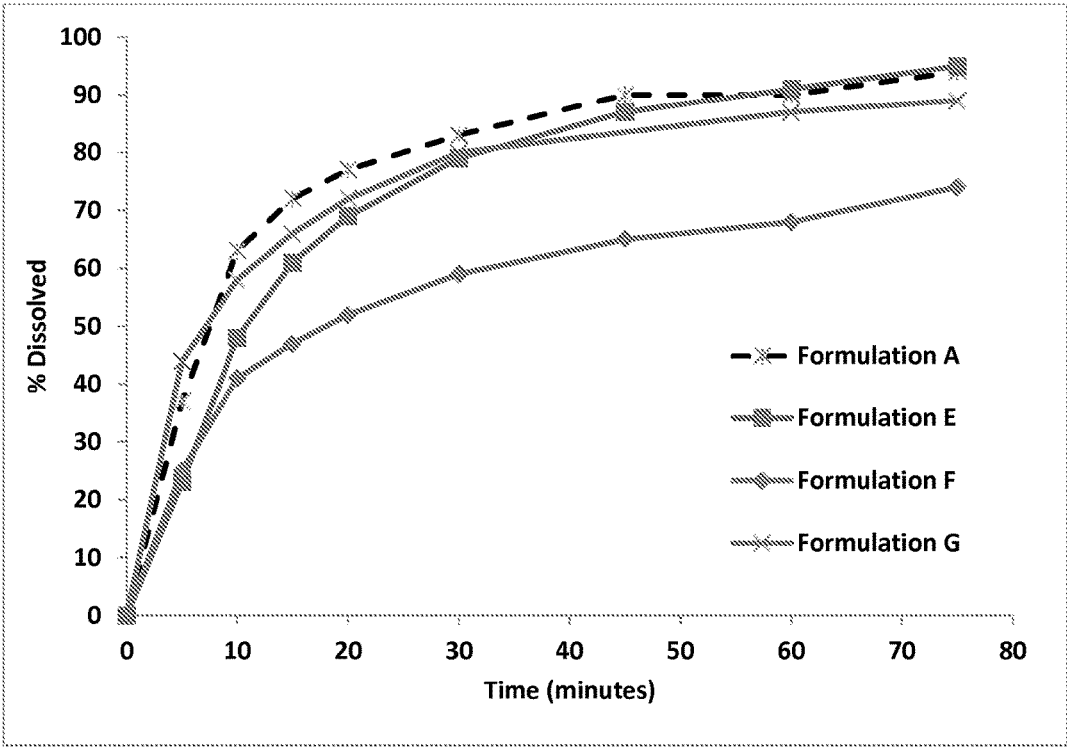


FIG 4.



NOVEL FORMULATIONS OF A BRUTON'S TYROSINE KINASE INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of U.S. patent application Ser. No. 15/370,535, filed Dec. 6, 2016, which is a continuation of U.S. patent application Ser. No. 14/821,290, filed Aug. 7, 2015, which claims the benefit of U.S. Provisional Application No. 62/034,353, filed Aug. 7, 2014, both of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] Described herein is the Bruton's tyrosine kinase (Btk) inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib), including novel pharmaceutical formulations thereof, as well as pharmaceutical compositions that include the Btk inhibitor and methods of using the Btk inhibitor in the treatment of diseases or conditions that would benefit from inhibition of Btk activity.

BACKGROUND OF THE INVENTION

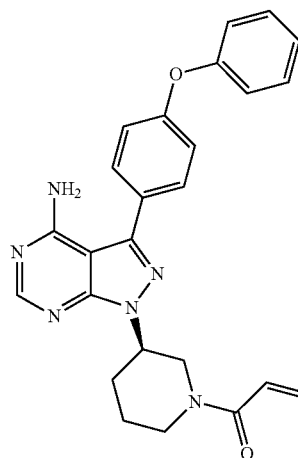
[0003] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0004] Btk is a key regulator of B-cell development, activation, signaling, and survival. In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF- α production in macrophages, IgE receptor (Fc ϵ RI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

[0005] 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is also known by its IUPAC name as 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl)prop-2-en-1-one or 2-Propen-1-one, 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl)-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein.

SUMMARY OF THE INVENTION

[0006] Described herein is the Btk inhibitor 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib) (Formula (I)) (Compound 1):



(I)

including pharmaceutical formulations, and methods of uses thereof. Also described are pharmaceutically acceptable compositions of the Btk inhibitor, and methods of uses thereof 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, as well as the pharmaceutically acceptable salts thereof, are used in the manufacture of medicaments for the treatment of diseases or conditions that are associated with Btk activity. 1-((R)-3-(4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one is an irreversible Btk inhibitor.

[0007] Also described herein are methods for preparing pharmaceutical formulations of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one. Further described are pharmaceutical compositions that include the novel formulations and methods of using the Btk inhibitor in the treatment of diseases or conditions (including diseases or conditions wherein irreversible inhibition of Btk provides therapeutic benefit to a mammal having the disease or condition).

[0008] Thus, in one aspect, the present invention provides solid dispersion pharmaceutical composition comprising solid dispersed ibrutinib.

[0009] In another aspect, the present invention provides solid dispersion pharmaceutical composition comprising solid dispersed ibrutinib, and the solid dispersed ibrutinib is spray-dried ibrutinib and the spray-dried ibrutinib is as defined herein.

[0010] In yet another aspect, the present invention provides solid dispersion formulations comprising solid dispersion pharmaceutical compositions as described herein, and a pharmaceutically acceptable carrier.

[0011] In one embodiment, the formulation is in a form of a tablet, a pill, a capsule, a powder, or a liquid.

[0012] In another embodiment, the formulation is for oral administration.

[0013] In yet another embodiment, the formulation is a modified release formulation, a controlled release formulation, a sustained release formulation, or an immediate release formulation.

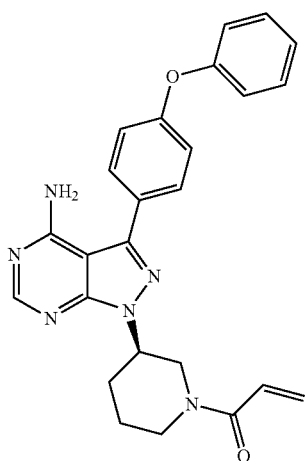
[0014] In certain embodiments, the formulation or composition provides improved pharmacokinetics (PK) properties as compared to the capsule formulation; and the capsule formulation comprises ibrutinib that is not in a solid dis-

persed composition. In one embodiment, the PK properties include drug exposure (C_{max}), and area under the curve (AUC). In certain embodiments, the formulation or composition provides reduced PK variability as compared to the capsule formulation.

[0015] In yet another specific aspect, the present invention provides methods to treat diseases or conditions using the composition and formulation of the present invention.

[0016] Exemplary diseases or conditions include an autoimmune disease or condition.

[0017] In one aspect is a solid dispersion pharmaceutical composition comprising solid dispersed ibrutinib, wherein ibrutinib is a compound of formula (I),



(I)

[0018] In one embodiment is a pharmaceutical composition, wherein the solid dispersed ibrutinib is a spray-dried ibrutinib composition. In another embodiment, the spray-dried ibrutinib composition comprises ibrutinib dispersed into one or more solubility enhancers. In a further embodiment, the solubility enhancer is a polymer matrix; and the polymer matrix comprises one or more polymers. In one embodiment, the spray-dried ibrutinib composition comprises 1-90 w/w ibrutinib dispersed into the polymer matrix. In yet another embodiment, the spray-dried ibrutinib composition comprises about 20% w/w ibrutinib dispersed into the polymer matrix. In a further embodiment, the spray-dried ibrutinib composition comprises about 50% w/w ibrutinib dispersed into the polymer matrix. In one embodiment, the spray-dried ibrutinib composition comprises about 70% w/w of ibrutinib dispersed into the polymer matrix.

[0019] In another embodiment, the spray-dried ibrutinib composition comprises about 80% w/w of ibrutinib dispersed into the polymer matrix. In yet another embodiment, the polymer in the polymer matrix is a linear polymer, a cross-linked polymer, a co-polymer, a graft polymer; or any combination thereof. In one embodiment, the polymer in the polymer matrix is hydrophilic. In another embodiment, the polymer in the polymer matrix is a non-ionic polymer. In a further embodiment, the polymer in the polymer matrix is hypromellose, copovidone, or povidone. In yet a further embodiment, the polymer in the polymer matrix is an ionic polymer. In one embodiment, the polymer in the polymer matrix is a cellulose based polymer. In another embodiment, the polymer in the polymer matrix is hydroxypropylcellu-

lose acetate-succinate, hydroxypropyl methyl cellulose phthalate, or cellulose acetate phthalate. In one embodiment, the polymer in the polymer matrix is hydroxypropyl cellulose, or hydroxypropylmethyl cellulose. In another embodiment, the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate. In yet another embodiment, the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS). In a further embodiment, the polymer has a molecular weight in a range of about 2,000 to about 500,000 daltons, about 100,000 to about 200,000 daltons, about 200,000 to about 300,000 daltons, or about 400,000 to about 500,000 daltons. In yet a further embodiment, the polymer in polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®). In one embodiment, the polymer in polymer matrix is polyvinylpyrrolidone/vinyl acetate copolymer, optionally in combination with polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®).

[0020] In one aspect is a solid dispersion formulation comprising a solid dispersion pharmaceutical composition described above and a pharmaceutically acceptable carrier. In one embodiment, the solid dispersion formulation is in a form of a liquid formulation or a solid formulation. In another embodiment, the solid dispersion formulation is in a form of a powder, dry powder, or a lyophilized powder. In yet another embodiment, the solid dispersion formulation is in a form of a suspension, a hydrogel, an emulsion, a liposome, or a micelle. In a further embodiment, the solid dispersion formulation is in a form of an aqueous suspension. In yet a further embodiment, the solid dispersion formulation is in a form of an organic suspension.

[0021] In one aspect is a solid dispersion formulation comprising a solid dispersion pharmaceutical composition described herein and one or more excipients. In one embodiment, the excipient comprises present in an amount from about 10 to about 50% w/w. In another embodiment, the excipient comprises cellulose. In yet another embodiment, the excipient comprises lactose. In a further embodiment, the excipient comprises lactose; and lactose is present in an amount from about 5 to about 20%, about 10 to about 20%, or about 14 to about 19% w/w. In yet a further embodiment, the excipient comprises microcrystalline cellulose. In one embodiment, the excipient comprises microcrystalline cellulose; and microcrystalline cellulose is present in an amount from about 20 to about 30%, about 23 to about 28%, or about 24 to about 26% w/w. In another embodiment, the excipient comprises a disintegrating agent. In a further embodiment, the excipient comprises croscarmellose sodium or sodium starch glycolate. In yet another embodiment, the excipient comprises croscarmellose sodium; and croscarmellose sodium is present in an amount from about 3 to about 9%, about 4 to about 8%, or about 5 to about 7% w/w. In one embodiment, the formulation comprises lactose, microcrystalline cellulose, and croscarmellose sodium. In another embodiment, the formulation comprises lactose, microcrystalline cellulose, and croscarmellose sodium; and lactose is present in an amount from about 5 to about 20%, about 10 to about 20%, or about 14 to about 19% w/w; microcrystalline cellulose is present in an amount from about 20 to about 30%, about 23 to about 28%, or about 24 to about 26% w/w; and croscarmellose sodium is present in an amount from about 3 to about 9%, about 4 to about 8%, or about 5 to about 7% w/w. In one embodiment, the

formulation further comprises one or more glidants. In a further embodiment, the glidant is silica (colloidal silicon dioxide). In yet a further embodiment, the glidant is silica (colloidal silicon dioxide); and silica (colloidal silicon dioxide) is present in an amount from about 0.5 to about 1.5%, about 0.7 to about 1.3%, or about 0.9 to about 1.1% w/w. In one embodiment, the formulation further comprises one or more lubricants. In another embodiment, the lubricant is magnesium stearate or sodium stearyl fumarate. In one embodiment, the lubricant is magnesium stearate; and magnesium stearate is present in an amount from about 0.1 to about 0.5%, or about 0.2 to about 0.3% w/w. In another embodiment is a solid dispersion formulation wherein the solid dispersion is in an amount from about 30 to about 65%, about 45 to about 55%, about 50 to about 55%, or about 50 to about 54% w/w.

[0022] In one embodiment, the formulation comprises

[0023] a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,

[0024] b) about 16 to about 18% w/w of lactose,

[0025] c) about 24 to about 26% w/w of microcrystalline cellulose,

[0026] d) about 5 to about 7% w/w of croscarmellose sodium,

[0027] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

[0028] f) about 0.2 to about 0.8% w/w of magnesium stearate;

[0029] and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

[0030] In another embodiment, the formulation comprises

[0031] a) about 52 to about 54% w/w of 20% active spray-dried ibrutinib,

[0032] b) about 13 to about 15% w/w of lactose,

[0033] c) about 24 to about 26% w/w of microcrystalline cellulose,

[0034] d) about 5 to about 7% w/w of croscarmellose sodium,

[0035] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

[0036] f) about 0.4 to about 0.6% w/w of magnesium stearate;

[0037] and wherein the 20% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 20% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

[0038] In a further embodiment, the HPMCAS is medium grade HPMCAS.

[0039] In yet a further embodiment, the formulation comprises

[0040] a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,

[0041] b) about 16 to about 18% w/w of lactose,

[0042] c) about 24 to about 26% w/w of microcrystalline cellulose,

[0043] d) about 5 to about 7% w/w of croscarmellose sodium,

[0044] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

[0045] f) about 0.2 to about 0.8% w/w of magnesium stearate;

[0046] and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®).

[0047] In another embodiment, the formulation comprises **[0048]** a) about 30 to about 50% w/w of the solid dispersion pharmaceutical composition,

[0049] b) about 20 to about 25% w/w of an excipient mixture comprising microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate,

[0050] c) about 0.2 to about 0.8% w/w of sodium stearyl fumarate, and

[0051] d) about 25 to about 35% w/w of crospovidone.

[0052] In one embodiment, the formulation comprises

[0053] a) about 45 to about 48% w/w of 33% active spray-dried ibrutinib,

[0054] b) about 20 to about 25% w/w of an excipient mixture comprising microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate,

[0055] c) about 0.2 to about 0.8% w/w of sodium stearyl fumarate, and

[0056] d) about 25 to about 35% w/w of crospovidone, and wherein the 33% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising 33% w/w of ibrutinib dispersed into a polymer matrix.

[0057] In yet another embodiment, the formulation comprises

[0058] a) about 30 to about 33% w/w of 50% active spray-dried ibrutinib,

[0059] b) about 20 to about 25% w/w of an excipient mixture comprising microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate, such as Prosolv® EasyTab,

[0060] c) about 0.2 to about 0.8% w/w of sodium stearyl fumarate, and

[0061] d) about 25 to about 35% w/w of crospovidone, and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising 50 w/w of ibrutinib dispersed into a polymer matrix.

[0062] In one embodiment, the formulation is in an oral dosage form containing a therapeutically effective amount of ibrutinib. In another embodiment, the formulation is in a form of a tablet, a pill, a capsule, a liquid, a modified release formulation, a controlled release formulation, a sustained release formulation, an immediate release formulation, or a powder. In yet another embodiment is a pharmaceutical composition or the spray-dried formulation described herein, wherein the pharmaceutical composition or formulation provides improved pharmacokinetics (PK) properties as compared to a capsule formulation comprising ibrutinib that is not in a solid dispersed composition. In another embodiment is a pharmaceutical composition or the spray-dried formulation described herein, wherein the pharmaceutical composition or formulation provides 2-25 fold increase in drug exposure as compared to a capsule formulation comprising ibrutinib that is not in a solid dispersed composition. In a further embodiment is a pharmaceutical composition or the spray-dried formulation described herein,

wherein the pharmaceutical composition or formulation provides 3-20 fold increase in drug exposure as compared to a capsule formulation comprising ibrutinib that is not in a solid dispersed composition. In a further embodiment is a pharmaceutical composition or the spray-dried formulation described herein, wherein the pharmaceutical composition or formulation provides reduced PK variability as compared to a capsule formulation comprising ibrutinib that is not in a solid dispersed composition.

[0063] In a further embodiment is a pharmaceutical composition or the spray-dried formulation described herein, wherein the capsule formulation comprises:

[0064] a) about 42 to about 43% of ibrutinib that is not in a solid dispersed ibrutinib composition,

[0065] b) about 4 to about 5% w/w of surfactant SLS®,

[0066] c) about 45 to about 46% w/w of microcrystalline cellulose,

[0067] d) about 6 to about 7% w/w of croscarmellose sodium, and

[0068] e) about 0.4 to about 0.5% w/w of magnesium stearate.

[0069] In one aspect is a method of treating a disease in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition or formulation described herein. In one embodiment is a method for treating an autoimmune disease or condition comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition or a formulation described herein. In one embodiment, the autoimmune disease is selected from rheumatoid arthritis or lupus. In another embodiment is a method for treating a heteroimmune disease or condition comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition or a formulation described herein.

[0070] In another aspect is a method for treating a cancer comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition or a formulation described herein. In one embodiment, the cancer is a B-cell proliferative disorder. In one embodiment, the B-cell proliferative disorder is diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia. In one embodiment, the cancer is a B cell malignancy. In one embodiment, the cancer is a B cell malignancy selected from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B Cell lymphoma (DLBCL), and multiple myeloma. In one embodiment, the cancer is a lymphoma, leukemia or a solid tumor. In one embodiment, the cancer is diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In another embodiment is a method for treating mastocytosis comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition or a formulation described herein. In another embodiment is a method for treating

osteoporosis or bone resorption disorders comprising administering to a patient in need a therapeutically effective amount of a pharmaceutical composition or a formulation described herein. In one embodiment is a method for treating an inflammatory disease or condition comprising administering to a patient in need a therapeutically effective amount of a pharmaceutical composition or a formulation described herein. In one embodiment is a method for treating lupus comprising administering to a patient in need a therapeutically effective amount of a pharmaceutical composition or a formulation described herein. In another embodiment is a method for treating a heteroimmune disease or condition comprising administering to a patient in need a therapeutically effective amount of a pharmaceutical composition or a formulation described herein.

[0071] Other objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present disclosure will become apparent to those skilled in the art from this detailed description. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

INCORPORATION BY REFERENCE

[0072] All publications and patent applications mentioned in this specification are herein incorporated by reference to the extent applicable and relevant.

BRIEF DESCRIPTION OF THE FIGURES

[0073] FIG. 1. shows mean plasma concentration-time profiles of ibrutinib following single oral dose administration of different ibrutinib formulations to fasted beagle dogs (Dose=140 mg) (Formulation A—capsule formulation; Formulation B, C, and D—Spray-dried formulations).

[0074] FIG. 2. shows mean plasma concentration-time profiles of ibrutinib following single oral dose administration of different ibrutinib formulations to fasted beagle dogs (Dose=140 mg) (Formulation A—capsule formulation; Formulation E, F, and G—Spray-dried formulations).

[0075] FIG. 3. illustrates the dissolution of the solid dispersion tablet Formulations B, C, and D as compared to the capsule formulation (Formulation A).

[0076] FIG. 4. illustrates the dissolution of the solid dispersion tablet Formulations E, F and G as compared to the capsule formulation (Formulation A).

DETAILED DESCRIPTION OF THE INVENTION

Certain Terminology

[0077] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed

description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “include,” “includes,” and “included,” is not limiting.

[0078] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0079] The term “about” when used before a numerical value indicates that the value may vary within a reasonable range, such as within $\pm 10\%$, $\pm 5\%$ or $\pm 1\%$ of the stated value.

[0080] As used herein, the term “comprising” is intended to mean that the compositions and methods, etc., include the recited elements, but do not exclude others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the intended use, but not excluding elements that do not materially affect the characteristic(s) of the compositions or methods. “Consisting of” shall mean excluding elements not specifically recited. Embodiments defined by each of these transition terms are within the scope of this invention.

[0081] The term “acceptable” or “pharmaceutically acceptable”, with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated or does not abrogate the biological activity or properties of the compound, and is relatively nontoxic.

[0082] As used herein, the term “agonist” refers to a compound, the presence of which results in a biological activity of a protein that is the same as the biological activity resulting from the presence of a naturally occurring ligand for the protein, such as, for example, Btk.

[0083] As used herein, the term “partial agonist” refers to a compound the presence of which results in a biological activity of a protein that is of the same type as that resulting from the presence of a naturally occurring ligand for the protein, but of a lower magnitude.

[0084] As used herein, the term “antagonist” refers to a compound, the presence of which results in a decrease in the magnitude of a biological activity of a protein. In certain embodiments, the presence of an antagonist results in complete inhibition of a biological activity of a protein, such as, for example, Btk. In certain embodiments, an antagonist is an inhibitor.

[0085] As used herein, “amelioration” of the symptoms of a particular disease, disorder or condition by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the compound or composition.

[0086] “Bioavailability” refers to the percentage of Compound 1 dosed that is delivered into the general circulation of the animal or human being studied. The total exposure ($AUC_{(0-\infty)}$) of a drug when administered intravenously is usually defined as 100% bioavailable (F %). “Oral bioavailability” refers to the extent to which Compound 1 is absorbed into the general circulation when the pharmaceutical composition is taken orally as compared to intravenous injection.

[0087] “Blood plasma concentration” refers to the concentration of Compound 1 in the plasma component of blood of a subject. It is understood that the plasma concentration of Compound 1 may vary significantly between subjects, due to variability with respect to metabolism and/or possible interactions with other therapeutic agents. In accordance with one embodiment disclosed herein, the blood plasma concentration of Compound 1 may vary from subject to subject. Likewise, values such as maximum plasma concentration (C_{max}) or time to reach maximum plasma concentration (T_{max}), or total area under the plasma concentration time curve ($AUC_{(0-\infty)}$) may vary from subject to subject. Due to this variability, the amount necessary to constitute “a therapeutically effective amount” of Compound 1 may vary from subject to subject.

[0088] The term “Bruton’s tyrosine kinase,” as used herein, refers to Bruton’s tyrosine kinase from *Homo sapiens*, as disclosed in, e.g., U.S. Pat. No. 6,326,469 (GenBank Accession No. NP_000052).

[0089] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0090] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition including a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms without undue adverse side effects. An appropriate “effective amount” in any individual case may be determined using techniques, such as a dose escalation study. The term “therapeutically effective amount” includes, for example, a prophylactically effective amount. An “effective amount” of a compound disclosed herein is an amount effective to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. It is understood that “an effect amount” or “a therapeutically effective amount” can vary from subject to subject, due to variation in metabolism of Compound 1, age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician. By way of example only, therapeutically effective amounts may be determined by routine experimentation, including but not limited to a dose escalation clinical trial.

[0091] The terms “enhance” or “enhancing” means to increase or prolong either in potency or duration a desired

effect. By way of example, “enhancing” the effect of therapeutic agents refers to the ability to increase or prolong, either in potency or duration, the effect of therapeutic agents on during treatment of a disease, disorder or condition. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of a therapeutic agent in the treatment of a disease, disorder or condition. When used in a patient, amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient’s health status and response to the drugs, and the judgment of the treating physician.

[0092] The terms “inhibits”, “inhibiting”, or “inhibitor” of a kinase, as used herein, refer to inhibition of enzymatic phosphotransferase activity.

[0093] The term “irreversible inhibitor,” as used herein, refers to a compound that, upon contact with a target protein (e.g., a kinase) causes the formation of a new covalent bond with or within the protein, whereby one or more of the target protein’s biological activities (e.g., phosphotransferase activity) is diminished or abolished notwithstanding the subsequent presence or absence of the irreversible inhibitor.

[0094] The term “irreversible Btk inhibitor,” as used herein, refers to an inhibitor of Btk that can form a covalent bond with an amino acid residue of Btk. In one embodiment, the irreversible inhibitor of Btk can form a covalent bond with a Cys residue of Btk; in particular embodiments, the irreversible inhibitor can form a covalent bond with a Cys 481 residue (or a homolog thereof) of Btk or a cysteine residue in the homologous corresponding position of another tyrosine kinase.

[0095] The term “modulate,” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[0096] As used herein, the term “modulator” refers to a compound that alters an activity of a molecule. For example, a modulator can cause an increase or decrease in the magnitude of a certain activity of a molecule compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[0097] The term “prophylactically effective amount,” as used herein, refers that amount of a composition applied to a patient which will relieve to some extent one or more of the symptoms of a disease, condition or disorder being treated. In such prophylactic applications, such amounts may depend on the patient’s state of health, weight, and the like. It is considered well within the skill of the art for one to determine such prophylactically effective amounts by routine experimentation, including, but not limited to, a dose escalation clinical trial.

[0098] The term “subject” or “patient” as used herein, refers to an animal which is the object of treatment, obser-

vation or experiment. By way of example only, a subject may be, but is not limited to, a mammal including, but not limited to, a human.

[0099] The terms “treat,” “treating” or “treatment”, as used herein, include alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition. The terms “treat,” “treating” or “treatment”, include, but are not limited to, prophylactic and/or therapeutic treatments.

[0100] As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as inhibition of Btk, in an assay that measures such response.

[0101] As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

[0102] Pharmaceutical Compositions/Formulations

[0103] A pharmaceutical composition, as used herein, refers to a mixture of Compound 1 with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to a subject. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[0104] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. Compound 1 and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. Compound 1 and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0105] In some embodiments, amorphous Compound 1 is incorporated into pharmaceutical compositions to provide solid oral dosage forms, such as powders, immediate release formulations, controlled release formulations, fast melt formulations, tablets, capsules, pills, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate and controlled release formulations.

[0106] As used herein, the term “solid dispersion” refers to the dispersion of one or more active agents in a polymer matrix at solid state prepared by a variety of methods, including, but not limited to spray drying, the melting (fusion), solvent, or the melting-solvent method. More information on “solid dispersion may be found in “Pharmaceutical Solid Dispersion Technology” Edited by Muhammad J. Habib (Technomic Publishing).

[0107] As used herein, the term “spray-dried ibrutinib” refers to a solid dispersion comprising ibrutinib dispersed into a polymer matrix prepared by a spray drying process, such as rapidly removing the solvent from the solution of ibrutinib and the polymer by, e.g., spraying the solution into a drying gas flow. Suitable solvents include polar organic solvents, such as alcohols such as methanol, ethanol, n-propanol, isopropanol, and butanol; esters such as ethyl acetate and propyl acetate; ketones such as acetone, methylethylketone and methyl isobutyl ketone; acetonitrile, tetrahydrofuran, toluene, methylene chloride, and 1,1,1-trichloroethane.

[0108] As used herein, the term “1-90% active spray-dried ibrutinib” refers to a spray-dried ibrutinib composition comprising 1-90% w/w ibrutinib based on the total weight of the composition.

[0109] As used herein, the term “50% active spray-dried ibrutinib” refers to a spray-dried ibrutinib composition comprising about 50% w/w ibrutinib.

[0110] As used herein, the term “20% active spray-dried ibrutinib” refers to a spray-dried ibrutinib composition comprising about 20% w/w ibrutinib.

[0111] As used herein, the term “polymer matrix” refers to compositions comprising one or more polymers in which the active agent can be dispersed or included within the matrix.

[0112] As used herein, the term “% w/w” refers to the weight of the component based on the total weight of a composition comprising the component.

[0113] As used herein, the term “crystalline” refers to a solid that exhibits long-range order in three dimensions of at least about 100 repeat units in each dimension.

[0114] As used herein, the term “amorphous” refers to a solid that does not exhibit any long range order in the positions of the atoms, and is intended to include not only solid which has essentially no order, but also solid which may have some small degree of order, but the order is in less than three dimensions and/or is only over short distances. Crystalline and amorphous forms of a compound may be characterized by techniques known in the art such as powder x-ray diffraction (PXRD) crystallography, solid state NMR, or thermal techniques such as differential scanning calorimetry (DSC).

Solid Dispersed Ibrutinib

[0115] In one aspect, the present invention provides solid dispersion pharmaceutical compositions comprising solid dispersed ibrutinib.

[0116] In one embodiment, the solid dispersed ibrutinib composition is a spray-dried ibrutinib composition.

[0117] In one embodiment, the spray-dried ibrutinib composition comprises a spray-dried form of ibrutinib which is prepared or formed by dispersion of ibrutinib into one or more solubility enhancers.

[0118] In one embodiment, the solubility enhancer is a polymer matrix.

[0119] In one embodiment, the spray-dried ibrutinib composition comprises 1-90 w/w of ibrutinib dispersed into the polymer matrix. In another embodiment, the spray-dried ibrutinib composition comprises 10-90% w/w of ibrutinib dispersed into the polymer matrix. In another embodiment, the spray-dried ibrutinib composition comprises 20-80% w/w of ibrutinib dispersed into the polymer matrix. In another embodiment, the spray-dried ibrutinib composition comprises 30-70% w/w of ibrutinib dispersed into the poly-

mer matrix. In another embodiment, the spray-dried ibrutinib composition comprises 40-60% w/w of ibrutinib dispersed into the polymer matrix.

[0120] In a particular embodiment, the spray-dried ibrutinib composition comprises about 20% w/w of ibrutinib dispersed into the polymer matrix.

[0121] In another particular embodiment, the spray-dried ibrutinib composition comprises about 50% w/w of ibrutinib dispersed into the polymer matrix.

[0122] In a further particular embodiment, the spray-dried ibrutinib composition comprises 70% w/w of ibrutinib dispersed into the polymer matrix.

[0123] In a further particular embodiment, the spray-dried ibrutinib composition comprises 80% w/w of ibrutinib dispersed into the polymer matrix.

[0124] In one embodiment, the polymer in the polymer matrix comprises a linear polymer, a cross-linked polymer, a co-polymer, a graft polymer; or any combination thereof.

[0125] In another embodiment, the polymer in the polymer matrix is hydrophilic.

[0126] In another embodiment, the polymer in the polymer matrix is a non-ionic polymer.

[0127] Exemplary non-ionic polymers include hydroxypropylmethyl cellulose, polyvinylpyrrolidone, Plasdene, polyvinyl alcohol, poloxamer, polysorbate, polyvinylpyrrolidone/vinyl acetate co-polymer (PVP-VA) and polyethyleneglycols (PEGs).

[0128] In another embodiment, the polymer in the polymer matrix is hypromellose, copovidone, or povidone.

[0129] In another embodiment, the polymer in the polymer matrix is an ionic polymer.

[0130] In another embodiment, the polymer in the polymer matrix is a cellulose based polymer.

[0131] In another embodiment, the polymer in the polymer matrix is hydroxypropylcellulose; hydroxymethylcellulose; hydroxypropylmethylcellulose (HPMC), methylcellulose polymer, hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene hydroxyethylcellulose and/or carboxymethyl hydroxyethylcellulose, an acrylic polymer, such as acrylic acid, acrylamide, and maleic anhydride polymers and copolymers; or a blend thereof; or mixtures thereof.

[0132] In another embodiment, the polymer in the polymer matrix is hydroxypropylcellulose acetate-succinate, hydroxypropyl methyl cellulose phthalate, or cellulose acetate phthalate.

[0133] In another embodiment, the polymer in the polymer matrix is hydroxypropyl cellulose, or hydroxypropylmethyl cellulose.

[0134] In another embodiment, the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate. In one embodiment, the weight ratio of ibrutinib and the polymer is about 1:1. In another particular embodiment, the weight ratio of ibrutinib and the polymer is about 1:4.

[0135] In a particular embodiment, the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS). In one embodiment, HPMCAS is of grade L. In another embodiment, HPMCAS is of grade H. In a particular embodiment, HPMCAS is of grade M.

[0136] In another embodiment, the polymer has a molecular weight in a range of about 2,000 to about 500,000 daltons, about 10,000 to about 90,000 daltons, about 20,000 to about 70,000 daltons, about 30,000 to about 60,000 daltons, about 40,000 to about 50,000 daltons, or about

10,000 to about 20,000 daltons, about 20,000 to about 30,000 daltons, about 30,000 to about 40,000 daltons, about 40,000 to about 50,000 daltons, about 60,000 to about 70,000 daltons, about 70,000 to about 80,000 daltons, about 80,000 to about 90,000 daltons, about 90,000 to about 100,000 daltons, about 100,000 to about 150,000 daltons, about 150,000 to about 200,000 daltons, about 200,000 to about 250,000 daltons, about 250,000 to about 300,000 daltons, about 350,000 to about 400,000 daltons, about 400,000 to about 450,000 daltons, or about 450,000 to about 500,000 daltons.

[0137] In a particular embodiment, the polymer has a molecular weight of about 20,000.

[0138] In a particular embodiment, the polymer has a molecular weight of about 140,000.

[0139] In a particular embodiment, the polymer has a molecular weight of about 320,000.

[0140] In another particular embodiment, the polymer in polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®).

[0141] In another embodiment, the polymer in the polymer matrix is polyvinylpyrrolidone/vinyl acetate copolymer. In one embodiment, the weight ratio of ibuprofen and the polymer is about 1:2. In one embodiment, the weight ratio of ibuprofen and the polymer is about 1:1.

[0142] In another embodiment, the polymer in the polymer matrix is polyvinylpyrrolidone/vinyl acetate copolymer and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. In one embodiment, the weight ratio of ibuprofen, polyvinylpyrrolidone/vinyl acetate copolymer and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer is about 1:1:1.

[0143] In another embodiment, solid dispersed ibuprofen composition and in particular the spray-dried ibuprofen composition provides improved pharmacokinetics (PK) properties, such as higher AUC and/or reduced variability in the pharmacokinetics parameters among different subjects, as compared to the pure ibuprofen, and in particular, a crystalline form of ibuprofen.

[0144] In some embodiments, the spray dried ibuprofen composition is prepared by a process comprising spray drying a solution of ibuprofen and the polymer in an organic solvent, such as acetone, acetonitrile, methanol, ethanol, n-propanol, isopropanol, butanol ethyl acetate, propyl acetate, tetrahydrofuran, methylene chloride, toluene, 1,1,1-trichloroethane and methylethylketone, etc.

[0145] In some embodiments, provided is a process of preparing the spray dried ibuprofen composition described herein, which process comprises spray drying a solution of ibuprofen and the polymer in an organic solvent, such as acetone, acetonitrile, methanol, ethanol, n-propanol, isopropanol, butanol ethyl acetate, propyl acetate, tetrahydrofuran, methylene chloride, toluene, 1,1,1-trichloroethane and methylethylketone, etc.

Solid Dispersed Formulations

[0146] In another aspect, the present invention provides solid dispersion formulations comprising a solid dispersion pharmaceutical composition as described herein, and a pharmaceutically acceptable excipient.

[0147] In one embodiment, the formulation comprises a solid dispersed ibuprofen composition.

[0148] In one embodiment, the solid dispersed ibuprofen composition is a spray-dried ibuprofen composition.

[0149] In one embodiment, the spray-dried ibuprofen composition comprises a spray-dried form of ibuprofen which is prepared or formed by dispersion of ibuprofen into one or more solubility enhancers.

[0150] In one embodiment, the solubility enhancer is a polymer matrix.

[0151] In one embodiment, the spray-dried ibuprofen composition comprises 1-90 w/w of ibuprofen dispersed into the polymer matrix. In another embodiment, the spray-dried ibuprofen composition comprises 10-90% w/w of ibuprofen dispersed into the polymer matrix. In another embodiment, the spray-dried ibuprofen composition comprises 20-80% w/w of ibuprofen dispersed into the polymer matrix. In another embodiment, the spray-dried ibuprofen composition comprises 30-70% w/w of ibuprofen dispersed into the polymer matrix. In another embodiment, the spray-dried ibuprofen composition comprises 40-60% w/w of ibuprofen dispersed into the polymer matrix.

[0152] In a particular embodiment, the spray-dried ibuprofen composition comprises about 20% w/w of ibuprofen dispersed into the polymer matrix.

[0153] In another particular embodiment, the spray-dried ibuprofen composition comprises about 50% w/w of ibuprofen dispersed into the polymer matrix.

[0154] In a further particular embodiment, the spray-dried ibuprofen composition comprises about 70% w/w of ibuprofen dispersed into the polymer matrix.

[0155] In a further particular embodiment, the spray-dried ibuprofen composition comprises about 80% w/w of ibuprofen dispersed into the polymer matrix.

[0156] In one embodiment, the polymer in the polymer matrix comprises a linear polymer, a cross-linked polymer, a copolymer, a graft polymer; or any combination thereof.

[0157] In another embodiment, the polymer in the polymer matrix is hydrophilic.

[0158] In another embodiment, the polymer in the polymer matrix is a non-ionic polymer.

[0159] Exemplary non-ionic polymers include hydroxypropylmethyl cellulose, polyvinylpyrrolidone, Pladone, polyvinyl alcohol, Pluronic, Tweens and Polyethyleneglycols (PEGs)

[0160] In another embodiment, the polymer in the polymer matrix is hypromellose, copovidone, or povidone.

[0161] In another embodiment, the polymer in the polymer matrix is an ionic polymer.

[0162] In another embodiment, the polymer in the polymer matrix is a cellulose based polymer.

[0163] In another embodiment, the polymer in the polymer matrix is hydroxypropylcellulose; hydroxymethylcellulose; hydroxypropylmethylcellulose (HPMC), methylcellulose polymer, hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene hydroxyethylcellulose and/or carboxymethyl hydroxyethylcellulose, an acrylic polymer, such as acrylic acid, acrylamide, and maleic anhydride polymers and copolymers; or a blend thereof; or mixtures thereof.

[0164] In another embodiment, the polymer in the polymer matrix is hydroxypropylcellulose acetate-succinate, hydroxypropyl methyl cellulose phthalate, or cellulose acetate phthalate.

[0165] In another embodiment, the polymer in the polymer matrix is hydroxypropyl cellulose, or hydroxypropylmethyl cellulose.

[0166] In another embodiment, the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate.

[0167] In a particular embodiment, the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

[0168] In another embodiment, the polymer has a molecular weight in a range of about 2,000 to about 100,000 daltons, about 10,000 to about 90,000 daltons, about 20,000 to about 70,000 daltons, about 30,000 to about 60,000 daltons, about 40,000 to about 50,000 daltons, or about 10,000 to about 20,000 daltons, about 20,000 to about 30,000 daltons, about 30,000 to about 40,000 daltons, about 40,000 to about 50,000 daltons, about 60,000 to about 70,000 daltons, about 70,000 to about 80,000 daltons, about 80,000 to about 90,000 daltons, or about 90,000 to about 100,000 daltons, about 100,000 to about 150,000 daltons, about 150,000 to about 200,000 daltons, about 200,000 to about 250,000 daltons, about 250,000 to about 300,000 daltons, about 350,000 to about 400,000 daltons, about 400,000 to about 450,000 daltons, or about 450,000 to about 500,000 daltons.

[0169] In a particular embodiment, the polymer has a molecular weight of about 20,000.

[0170] In a particular embodiment, the polymer has a molecular weight of about 140,000.

[0171] In a particular embodiment, the polymer has a molecular weight of about 320,000.

[0172] In another particular embodiment, with respect to the formulation, the polymer in polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®).

[0173] In one embodiment, the solid dispersion formulation is in a form of a liquid formulation or a solid formulation.

[0174] In another embodiment, the solid dispersion formulation is in a form of a powder, dry powder, or a lyophilized powder.

[0175] In another embodiment, the solid dispersion formulation is in a form of a suspension, a hydrogel, an emulsion, a liposome, or a micelle.

[0176] In another embodiment, the solid dispersion formulation is in a form of an aqueous suspension.

[0177] In another embodiment, the solid dispersion formulation is in a form of an organic suspension.

[0178] In one embodiment, the solid dispersed ibrutinib composition (including ibrutinib and the matrix) is present in the formulation in an amount from about 10 to about 90%, about 20 to about 80%, about 30 to about 70%, about 40 to about 55% w/w of the formulation.

[0179] In another embodiment, the formulation comprises one or more excipients.

[0180] Exemplary excipients used in the nanoparticle formulation can be found in "Handbook of Pharmaceutical Excipients" Rowe et al., editors, 7th edition, Pharmaceutical Press, London, 2012.

[0181] In certain embodiments, the excipients are selected from diluents, disintegrating agents, or surfactants, or a combination thereof.

[0182] In certain embodiments, the excipients are selected from a group consisting of a polymer, a copolymer, and an anionic surfactant.

[0183] In some embodiments, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, cal-

cium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc. In some embodiments the diluent is microcrystalline cellulose. In some embodiments, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some embodiments, the disintegrating agent is croscarmellose sodium. In some embodiments, the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, poloxomers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide. In some embodiments, the surfactant is sodium lauryl sulfate.

[0184] In certain embodiments, the excipient is present in an amount from about 10 to about 50% w/w.

[0185] In certain embodiments, the excipient comprises cellulose.

[0186] In one embodiment, the excipient comprises lactose.

[0187] In another embodiment, the excipient comprises lactose; and lactose is present in an amount from about 0 to about 80% w/w. In another embodiment, lactose is present in an amount from about 5 to about 20%, about 10 to about 20%, or about 14 to about 19% w/w. In a particular embodiment, lactose is present in an amount of about 14%, about 15%, about 16%, about 17%, about 18%, or about 19% w/w, or any range between two of the values, end points inclusive.

[0188] In another embodiment, the excipient comprises microcrystalline cellulose.

[0189] In another embodiment, the excipient comprises microcrystalline cellulose; and microcrystalline cellulose is present in an amount from about 0 to about 80% w/w. In another embodiment, microcrystalline cellulose is present in an amount from about 20 to about 30%, about 23 to about 28%, or about 24 to about 26% w/w. In a particular embodiment, microcrystalline cellulose is present in an amount of about 23%, about 24%, about 25%, about 26%, or about 27% w/w, or any range between two of the values, end points inclusive.

[0190] In another embodiment, the excipient comprises croscarmellose sodium.

[0191] In another embodiment, the excipient comprises croscarmellose sodium; and croscarmellose sodium is present in an amount from about 3 to about 9%, about 4 to about 8%, or about 5 to about 7% w/w. In a particular embodiment, croscarmellose sodium is present in an amount of about 4%, about 5%, about 6%, about 7%, or about 8% w/w, or any range between two of the values, end points inclusive.

[0192] In another embodiment, the formulation comprises lactose, microcrystalline cellulose, and croscarmellose sodium.

[0193] In a particular embodiment, the formulation comprises lactose, microcrystalline cellulose, and croscarmellose sodium; and

[0194] lactose is present in an amount from about 5 to about 20%, about 10 to about 20%, or about 14 to about 19% w/w;

- [0195] microcrystalline cellulose is present in an amount from about 20 to about 30%, about 23 to about 28%, or about 24 to about 26% w/w; and
- [0196] croscarmellose sodium is present in an amount from about 3 to about 9%, about 4 to about 8%, or about 5 to about 7% w/w.
- [0197] In another embodiment, the formulation further comprises one or more glidants.
- [0198] In another embodiment, the glidant is silica (colloidal silicon dioxide).
- [0199] In another embodiment, the glidant is silica (colloidal silicon dioxide); and glidant or silica (colloidal silicon dioxide) is present in an amount from about 0.5 to about 1.5%, about 0.7 to about 1.3%, or about 0.9 to about 1.1% w/w. In a particular embodiment, silica is present in an amount of about 0.5%, 1%, or 1.5% w/w, or any range between two of the values, end points inclusive.
- [0200] In another embodiment, the formulation further comprises one or more lubricants.
- [0201] In some embodiments, the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumarate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes. In some embodiments, the lubricant is magnesium stearate.
- [0202] In another embodiment, the lubricant is magnesium stearate; and lubricant or magnesium stearate is present in an amount from about 0.1 to about 0.5%, or about 0.2 to about 0.3% w/w.
- [0203] In another embodiment, the solid dispersion of ibrutinib is in an amount from about 30 to about 65%, about 45 to about 55%, about 50 to about 55%, or about 50 to about 54% w/w. In a particular embodiment, the solid dispersion is present in an amount of about 30%, 33%, 40%, 48%, 49%, 50%, 51%, 52%, 53% or 54% w/w, or any range between two of the values, end point inclusive.
- [0204] In a particular embodiment, the formulation (Formulation C) comprises
- [0205] a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,
- [0206] b) about 16 to about 18% w/w of lactose,
- [0207] c) about 24 to about 26% w/w of microcrystalline cellulose,
- [0208] d) about 5 to about 7% w/w of croscarmellose sodium,
- [0209] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and
- [0210] f) about 0.2 to about 0.8% w/w or about 0.2 to about 0.3% w/w of magnesium stearate;
- [0211] and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).
- [0212] In another particular embodiment, the formulation (Formulation D) comprises
- [0213] a) about 52 to about 54% w/w of 20% active spray-dried ibrutinib,
- [0214] b) about 13 to about 15% w/w of lactose,
- [0215] c) about 24 to about 26% w/w of microcrystalline cellulose,
- [0216] d) about 5 to about 7% w/w of croscarmellose sodium,
- [0217] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and
- [0218] f) about 0.4 to about 0.6% w/w of magnesium stearate;
- [0219] and wherein the 20% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 20% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).
- [0220] In a particular embodiment, the HPMCAS is M grade HPMCAS.
- [0221] In another particular embodiment, the formulation (Formulation B) comprises
- [0222] a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,
- [0223] b) about 16 to about 18% w/w of lactose,
- [0224] c) about 24 to about 26% w/w of microcrystalline cellulose,
- [0225] d) about 5 to about 7% w/w of croscarmellose sodium,
- [0226] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and
- [0227] f) about 0.2 to about 0.8% w/w or about 0.2 to about 0.3% w/w of magnesium stearate;
- [0228] and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®).
- [0229] In another embodiment, the formulation is in an oral dosage form containing a therapeutically effective amount of spray-dried ibrutinib. In some embodiments, the pharmaceutical composition comprises about 0.5 mg to about 1000 mg of spray-dried ibrutinib.
- [0230] In another embodiment, the formulation is in a form of a tablet, a pill, a capsule, a liquid, or a powder. In another embodiment, the formulation is in a form of a modified release formulation. In another embodiment, the formulation is in a form of a controlled release formulation, a sustained release formulation, an immediate release formulation, an extended release formulation, a prolonged release formulation, targeted release formulation. In yet another embodiment, the formulation is in a form of a powder.
- [0231] In a further embodiment, the spray-dried ibrutinib is in amorphous form.
- [0232] In another embodiment, the pharmaceutical composition or formulation provides improved pharmacokinetics (PK) properties as compared to the capsule formulation (Formulation A); and the capsule formulation comprises:
- [0233] a) about 42 to about 43% w/w of ibrutinib,
- [0234] b) about 4 to about 5% w/w of surfactant (Sodium Lauryl Sulfate) SLS®,
- [0235] c) about 45 to about 46% w/w of microcrystalline cellulose,
- [0236] d) about 6 to about 7% w/w of croscarmellose sodium, and
- [0237] e) about 0.4 to about 0.5% w/w of magnesium stearate.
- [0238] In another embodiment, the pharmaceutical composition or formulation provides 2-25 fold increase in drug exposure as compared to the capsule formulation.

[0239] In another embodiment, the pharmaceutical composition or formulation provides 3-20 fold increase in drug exposure as compared to the capsule formulation.

[0240] In another embodiment, the pharmaceutical composition or formulation provides reduced PK variability as compared to the capsule formulation.

[0241] In some embodiments, provided herein is a pharmaceutical formulation (Formulation C) for oral administration comprising:

[0242] a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,

[0243] b) about 16 to about 18% w/w of lactose,

[0244] c) about 24 to about 26% w/w of microcrystalline cellulose,

[0245] d) about 5 to about 7% w/w of croscarmellose sodium,

[0246] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

[0247] f) about 0.2 to about 0.3% w/w of magnesium stearate;

[0248] and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

[0249] In some embodiments, provided herein is a pharmaceutical formulation (Formulation D) for oral administration comprising:

[0250] a) about 52 to about 54% w/w of 20% active spray-dried ibrutinib,

[0251] b) about 13 to about 15% w/w of lactose,

[0252] c) about 24 to about 26% w/w of microcrystalline cellulose,

[0253] d) about 5 to about 7% w/w of croscarmellose sodium,

[0254] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

[0255] f) about 0.4 to about 0.6% w/w of magnesium stearate;

[0256] and wherein the 20% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 20% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

[0257] In some embodiments, provided herein is a pharmaceutical formulation (Formulation B) for oral administration comprising:

[0258] a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,

[0259] b) about 16 to about 18% w/w of lactose,

[0260] c) about 24 to about 26% w/w of microcrystalline cellulose,

[0261] d) about 5 to about 7% w/w of croscarmellose sodium,

[0262] e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

[0263] f) about 0.2 to about 0.3% w/w of magnesium stearate;

and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising 50 w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®)

[0264] In some embodiments, provided herein is a pharmaceutical formulation for oral administration comprising:

[0265] a) about 30 to about 50% w/w of a spray-dried ibrutinib composition described herein,

[0266] b) about 20 to about 25% w/w of an excipient mixture comprising microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate, such as Prosolv® EasyTab;

[0267] c) about 0.2 to about 0.8% w/w of sodium stearyl fumarate, and

[0268] d) about 25 to about 35% w/w of crospovidone.

[0269] In some embodiments, provided herein is a pharmaceutical formulation for oral administration comprising:

[0270] a) about 45 to about 48% w/w of 33% active spray-dried ibrutinib,

[0271] b) about 20 to about 25% w/w of an excipient mixture comprising microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate, such as Prosolv® EasyTab,

[0272] c) about 0.2 to about 0.8% w/w of sodium stearyl fumarate, and

[0273] d) about 25 to about 35% w/w of crospovidone, and wherein the 33% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising 33% w/w of ibrutinib dispersed into a polymer matrix. In some embodiments, the polymer in the polymer matrix is polyvinylpyrrolidone/vinyl acetate co-polymer. In some embodiments, the polymer in the polymer matrix is a mixture of polyvinylpyrrolidone/vinyl acetate co-polymer and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, such as in a 2:1 to 1:2, e.g., 1:1 ratio.

[0274] In some embodiments, provided herein is a pharmaceutical formulation for oral administration comprising:

[0275] a) about 30 to about 33% w/w of 50% active spray-dried ibrutinib,

[0276] b) about 20 to about 25% w/w of an excipient mixture comprising microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate, such as Prosolv® EasyTab,

[0277] c) about 0.2 to about 0.8% w/w of sodium stearyl fumarate, and

[0278] d) about 25 to about 35% w/w of crospovidone, and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising 50 w/w of ibrutinib dispersed into a polymer matrix. In some embodiments, the polymer in the polymer matrix is polyvinylpyrrolidone/vinyl acetate co-polymer.

[0279] In another aspect the present invention provides formulations or compositions as described herein; wherein the formulation is in a unit dosage form in a blister pack, and said blister pack comprises metal or plastic foil. In one embodiment, the formulation is Formulation B. In another embodiment, the formulation is Formulation C. In a further embodiment, the formulation is Formulation D.

[0280] In another embodiment is a package comprising one or more discrete blister pockets, wherein each blister pocket comprises a unit dosage form comprising formulations or compositions as described herein. In one embodiment, the formulation is Formulation B. In another embodiment, the formulation is Formulation C. In a further embodiment, the formulation is Formulation D.

[0281] In one embodiment, a kit is provided which contains a multiplicity of oral dosage forms, such as tablets or capsules, packaging such as ajar containing the oral dosage

forms, and instructions for use to administer the oral dosage forms in accordance with the method described herein. Unit dose packaging such as blister packs provide a useful way of packaging the oral dosage form of the formulations described herein, and in other embodiments embody a kit when combined with instructions for use. In other embodiments, detailed product information are included with the instructions for use in the kit. Blister packaging is particularly useful with solid oral dosage forms and is in further embodiments useful for alternate day dosing schedules for example. In one embodiment, solid unit dosage forms of the formulations described herein included in a blister pack with instructions to administer one or more tablets or capsules on a daily basis so that the dosage of the formulations described herein are sufficiently administered. In another embodiment, solid unit dosage forms are included in a blister pack with instructions to administer one or more tablets or capsules on an alternate day basis so that the dosage per day is sufficiently administered.

Methods of Use

[0282] In one aspect, provided herein are methods for treating a patient by administering Compound 1. In some embodiments, provided herein is a method of inhibiting the activity of tyrosine kinase(s), such as Btk, or of treating a disease, disorder, or condition, which would benefit from inhibition of tyrosine kinase(s), such as Btk, in a mammal, which includes administering to the mammal a therapeutically effective amount of Compound 1, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate.

[0283] In another aspect, provided herein is the use of Compound 1 for inhibiting Bruton's tyrosine kinase (Btk) activity or for the treatment of a disease, disorder, or condition, which would benefit from inhibition of Bruton's tyrosine kinase (Btk) activity.

[0284] In some embodiments, amorphous Compound 1 is administered to a human.

[0285] In some embodiments, amorphous Compound 1 is orally administered.

[0286] In other embodiments, amorphous Compound 1 is used for the formulation of a medicament for the inhibition of tyrosine kinase activity. In some other embodiments, amorphous Compound 1 is used for the formulation of a medicament for the inhibition of Bruton's tyrosine kinase (Btk) activity.

[0287] In one aspect, provided herein is a method of treating cancer in a mammal comprising administering to the mammal a pharmaceutical composition or formulation described herein comprising Compound 1. In some embodiments, the cancer is a B cell malignancy. In some embodiments, the cancer is a B cell malignancy selected from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), diffuse large B Cell lymphoma (DLBCL), and multiple myeloma. In some embodiments, the cancer is a lymphoma, leukemia or a solid tumor. In some embodiments, the cancer is diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B

cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In some embodiments, where the subject is suffering from a cancer, an anti-cancer agent is administered to the subject in addition to one of the above-mentioned compounds. In one embodiment, the anti-cancer agent is an inhibitor of mitogen-activated protein kinase signaling

[0288] In one aspect, provided herein is a method of treating an inflammatory or an autoimmune disease in a mammal comprising administering to the mammal a pharmaceutical composition described herein comprising Compound 1. In some embodiments, the inflammatory disease is asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis. In some embodiments, the autoimmune disease is inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, Addison's disease, opso-clonus-myoclonus syndrome, ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, or vulvodinia.

[0289] Articles of manufacture including packaging material, Compound 1 within the packaging material, and a label that indicates that Compound 1 is used for inhibiting the activity of tyrosine kinase(s), such as Btk, are provided.

[0290] In a further aspect, provided herein is a method of treating an autoimmune disease in a mammal, comprising administering Compound 1 to the mammal.

[0291] In a further aspect, provided herein is a method of treating a heteroimmune disease or condition in a mammal, comprising administering Compound 1 to the mammal.

[0292] In a further aspect, provided herein is a method of treating an inflammatory disease in a mammal, comprising administering Compound 1 to the mammal.

[0293] In a further aspect, provided herein is a method of treating cancer in a mammal, comprising administering Compound 1 to the mammal.

[0294] In a further aspect, provided herein is a method of treating a thromboembolic disorder in a mammal, comprising administering Compound 1 to the mammal. Thromboembolic disorders include, but are not limited to, myocardial infarct, angina pectoris, reocclusion after angioplasty, rest-

enosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, or deep venous thrombosis.

[0295] In another aspect are methods for modulating, including irreversibly inhibiting the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with Compound 1, in a mammal comprising administering to the mammal at least once an effective amount of Compound 1. In another aspect are methods for modulating, including irreversibly inhibiting, the activity of Btk in a mammal comprising administering to the mammal at least once an effective amount of Compound 1. In another aspect are methods for treating Btk-dependent or Btk mediated conditions or diseases, comprising administering to the mammal at least once an effective amount of Compound 1.

[0296] In another aspect are methods for treating inflammation comprising administering to the mammal at least once an effective amount of Compound 1.

[0297] A further aspect are methods for the treatment of cancer comprising administering to the mammal at least once an effective amount of Compound 1. The type of cancer may include, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[0298] In another aspect are methods for treating respiratory diseases comprising administering to the mammal at least once an effective amount of Compound 1. In a further embodiment of this aspect, the respiratory disease is asthma. In a further embodiment of this aspect, the respiratory disease includes, but is not limited to, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma.

[0299] In another aspect are methods for preventing rheumatoid arthritis and/or osteoarthritis comprising administering to the mammal at least once an effective amount of Compound 1.

[0300] In another aspect are methods for treating inflammatory responses of the skin comprising administering to the mammal at least once an effective amount of Compound 1. Such inflammatory responses of the skin include, by way of example, dermatitis, contact dermatitis, eczema, urticaria, rosacea, and scarring. In another aspect are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering to the mammal an effective amount of Compound 1.

[0301] In another aspect is the use of Compound 1 in the manufacture of a medicament for treating an inflammatory disease or condition in an animal in which the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with at least one irreversible inhibitor described herein, contributes to the pathology and/or symptoms of the disease or condition. In one embodiment of this aspect, the tyrosine kinase protein is Btk. In another or further embodiment of this aspect, the inflammatory disease or conditions are respiratory, cardiovascular, or proliferative diseases.

[0302] In any of the aforementioned aspects are further embodiments in which Compound 1 is (a) systemically administered to the mammal; (b) administered orally to the mammal; (c) intravenously administered to the mammal; (d) administered by inhalation; (e) administered by nasal administration; or (f) administered by injection to the mammal; (g) administered topically (dermal) to the mammal; (h) administered by ophthalmic administration; or (i) administered rectally to the mammal.

[0303] In any of the aforementioned aspects are further embodiments comprising single administration of Compound 1, including further embodiments in which Compound 1 is administered (i) once; (ii) multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0304] In any of the aforementioned aspects are further embodiments comprising multiple administrations of Compound 1, including further embodiments in which (i) Compound 1 is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) Compound 1 is administered to the mammal every 8 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of Compound 1 is temporarily suspended or the dose of Compound 1 being administered is temporarily reduced; at the end of the drug holiday, dosing of Compound 1 is resumed. The length of the drug holiday can vary from 2 days to 1 year.

[0305] In some embodiments, in any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is: optically pure (i.e. greater than 99% chiral purity by HPLC). In some embodiments, in any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt or solvate thereof, is replaced with: a) Compound 1, or a pharmaceutically acceptable salt or solvate thereof, of lower chiral purity; b) 1-((S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, or a pharmaceutically acceptable salt or solvate thereof of any optical purity; or c) racemic 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one, or a pharmaceutically acceptable salt or solvate thereof.

[0306] In any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), amorphous Compound 1 is used. In any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), amorphous Compound 1 is used. In any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), amorphous Compound 1 is used; and the amorphous compound is in the spray-dried form.

[0307] In some embodiments, in any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt thereof, is replaced with an active metabolite of Compound 1. In some embodiments, the active metabolite is in a crystalline form. In some embodiments, the active metabolite is in an amorphous phase. In further embodiments the metabolite is isolated. In some embodiments, in any of the embodiments disclosed herein (including methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically accept-

able salt thereof, is replaced with a prodrug of Compound 1, or a deuterated analog of Compound 1, or a pharmaceutically acceptable salt thereof.

[0308] Other objects, features and advantages of the methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present disclosure will become apparent to those skilled in the art from this detailed description. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0309] The diverse roles played by Btk signaling in various hematopoietic cell functions, e.g., B-cell receptor activation, suggests that small molecule Btk inhibitors, such as Compound 1, are useful for reducing the risk of or treating a variety of diseases affected by or affecting many cell types of the hematopoietic lineage including, e.g., autoimmune diseases, heteroimmune conditions or diseases, inflammatory diseases, cancer (e.g., B-cell proliferative disorders), and thromboembolic disorders. Further, irreversible Btk inhibitor compounds, such as Compound 1, can be used to inhibit a small subset of other tyrosine kinases that share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with the irreversible inhibitor.

[0310] In some embodiments, Compound 1 can be used in the treatment of an autoimmune disease in a mammal, which includes, but is not limited to, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, lupus, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, and vulvodinia.

[0311] In some embodiments, Compound 1 can be used in the treatment of a heteroimmune disease or condition in a mammal, which include, but are not limited to graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[0312] In some embodiments, Compound 1 can be used in the treatment of an inflammatory disease in a mammal, which includes, but is not limited to asthma, inflammatory bowel disease, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermato-

myositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, and vulvitis.

[0313] In yet other embodiments, the methods described herein can be used to treat a cancer, e.g., B-cell proliferative disorders, which include, but are not limited to diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, and lymphomatoid granulomatosis.

[0314] In further embodiments, the methods described herein can be used to treat thromboembolic disorders, which include, but are not limited to myocardial infarct, angina pectoris (including unstable angina), reocclusions or restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischemia, peripheral arterial occlusive disorders, pulmonary embolisms, and deep venous thromboses.

Hematological Malignancies

[0315] Disclosed herein, in certain embodiments, is a method for treating a hematological malignancy in an individual in need thereof, comprising: administering to the individual an amount of Compound 1.

[0316] In some embodiments, the hematological malignancy is a non-Hodgkin's lymphoma (NHL). In some embodiments, the hematological malignancy is a chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the hematological malignancy is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia, multiple myeloma (MM), marginal zone lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, or extranodal marginal zone B cell lymphoma. In some embodiments, the hematological malignancy is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, acute lymphoblastic leukemia, or precursor B-cell acute lymphoblastic leukemia. In some embodiments, the hematological malignancy is chronic lymphocytic leukemia (CLL). In some embodiments, the hematological malignancy is mantle cell lymphoma (MCL). In some embodiments, the hematological malignancy is diffuse large B-cell lymphoma (DLBCL). In some embodiments, the hematological malignancy is diffuse large B-cell lymphoma (DLBCL), ABC subtype. In some embodiments, the hematological malignancy is diffuse large B-cell lymphoma (DLBCL), GCB subtype. In some embodiments, the hematological malignancy is Waldenström's macroglobulinemia (WM). In some embodiments, the hematological malignancy is multiple myeloma (MM). In some embodiments, the hematological malignancy is

Burkitt's lymphoma. In some embodiments, the hematological malignancy is follicular lymphoma (FL). In some embodiments, the hematological malignancy is transformed follicular lymphoma. In some embodiments, the hematological malignancy is marginal zone lymphoma.

[0317] In some embodiments, the hematological malignancy is relapsed or refractory non-Hodgkin's lymphoma (NHL). In some embodiments, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma (MCL), relapsed or refractory follicular lymphoma (FL), relapsed or refractory CLL, relapsed or refractory SLL, relapsed or refractory multiple myeloma, relapsed or refractory Waldenstrom's macroglobulinemia, relapsed or refractory multiple myeloma (MM), relapsed or refractory marginal zone lymphoma, relapsed or refractory Burkitt's lymphoma, relapsed or refractory non-Burkitt high grade B cell lymphoma, relapsed or refractory extranodal marginal zone B cell lymphoma. In some embodiments, the hematological malignancy is a relapsed or refractory acute or chronic myelogenous (or myeloid) leukemia, relapsed or refractory myelodysplastic syndrome, relapsed or refractory acute lymphoblastic leukemia, or relapsed or refractory precursor B-cell acute lymphoblastic leukemia. In some embodiments, the hematological malignancy is relapsed or refractory chronic lymphocytic leukemia (CLL). In some embodiments, the hematological malignancy is relapsed or refractory mantle cell lymphoma (MCL). In some embodiments, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In some embodiments, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), ABC subtype. In some embodiments, the hematological malignancy is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), GCB subtype. In some embodiments, the hematological malignancy is relapsed or refractory Waldenstrom's macroglobulinemia (WM). In some embodiments, the hematological malignancy is relapsed or refractory multiple myeloma (MM). In some embodiments, the hematological malignancy is relapsed or refractory Burkitt's lymphoma. In some embodiments, the hematological malignancy is relapsed or refractory follicular lymphoma (FL).

[0318] In some embodiments, the hematological malignancy is a hematological malignancy that is classified as high-risk. In some embodiments, the hematological malignancy is high risk CLL or high risk SLL.

[0319] B-cell lymphoproliferative disorders (BCLDs) are neoplasms of the blood and encompass, inter alia, non-Hodgkin lymphoma, multiple myeloma, and leukemia. BCLDs can originate either in the lymphatic tissues (as in the case of lymphoma) or in the bone marrow (as in the case of leukemia and myeloma), and they all are involved with the uncontrolled growth of lymphocytes or white blood cells. There are many subtypes of BCLD, e.g., chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL). The disease course and treatment of BCLD is dependent on the BCLD subtype; however, even within each subtype the clinical presentation, morphologic appearance, and response to therapy is heterogeneous.

[0320] Malignant lymphomas are neoplastic transformations of cells that reside predominantly within lymphoid tissues. Two groups of malignant lymphomas are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). Both

types of lymphomas infiltrate reticuloendothelial tissues. However, they differ in the neoplastic cell of origin, site of disease, presence of systemic symptoms, and response to treatment (Freedman et al., "Non-Hodgkin's Lymphomas" Chapter 134, Cancer Medicine, (an approved publication of the American Cancer Society, B. C. Decker Inc., Hamilton, Ontario, 2003).

[0321] Non-Hodgkin's Lymphomas

[0322] Disclosed herein, in certain embodiments, is a method for treating a non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1.

[0323] Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory non-Hodgkin's lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1. In some embodiments, the non-Hodgkin's lymphoma is relapsed or refractory diffuse large B-cell lymphoma (DLBCL), relapsed or refractory mantle cell lymphoma, relapsed or refractory follicular lymphoma, or relapsed or refractory CLL.

[0324] Non-Hodgkin lymphomas (NHL) are a diverse group of malignancies that are predominately of B-cell origin. NHL may develop in any organs associated with lymphatic system such as spleen, lymph nodes or tonsils and can occur at any age. NHL is often marked by enlarged lymph nodes, fever, and weight loss. NHL is classified as either B-cell or T-cell NHL. Lymphomas related to lymphoproliferative disorders following bone marrow or stem cell transplantation are usually B-cell NHL. In the Working Formulation classification scheme, NHL has been divided into low-, intermediate-, and high-grade categories by virtue of their natural histories (see "The Non-Hodgkin's Lymphoma Pathologic Classification Project," Cancer 49(1982): 2112-2135). The low-grade lymphomas are indolent, with a median survival of 5 to 10 years (Hornig and Rosenberg (1984) N. Engl. J. Med. 311:1471-1475). Although chemotherapy can induce remissions in the majority of indolent lymphomas, cures are rare and most patients eventually relapse, requiring further therapy. The intermediate- and high-grade lymphomas are more aggressive tumors, but they have a greater chance for cure with chemotherapy. However, a significant proportion of these patients will relapse and require further treatment.

[0325] A non-limiting list of the B-cell NHL includes Burkitt's lymphoma (e.g., Endemic Burkitt's Lymphoma and Sporadic Burkitt's Lymphoma), Cutaneous B-Cell Lymphoma, Cutaneous Marginal Zone Lymphoma (MZL), Diffuse Large Cell Lymphoma (DLBCL), Diffuse Mixed Small and Large Cell Lymphoma, Diffuse Small Cleaved Cell, Diffuse Small Lymphocytic Lymphoma, Extranodal Marginal Zone B-cell lymphoma, follicular lymphoma, Follicular Small Cleaved Cell (Grade 1), Follicular Mixed Small Cleaved and Large Cell (Grade 2), Follicular Large Cell (Grade 3), Intravascular Large B-Cell Lymphoma, Intravascular Lymphomatosis, Large Cell Immunoblastic Lymphoma, Large Cell Lymphoma (LCL), Lymphoblastic Lymphoma, MALT Lymphoma, Mantle Cell Lymphoma (MCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), extranodal marginal zone B-cell lymphoma-mucosa-associated lymphoid tissue (MALT) lymphoma, Mediastinal Large B-Cell Lymphoma, nodal marginal zone B-cell lymphoma,

splenic marginal zone B-cell lymphoma, primary mediastinal B-cell lymphoma, lymphoplasmocytic lymphoma, hairy cell leukemia, Waldenstrom's Macroglobulinemia, and primary central nervous system (CNS) lymphoma. Additional non-Hodgkin's lymphomas are contemplated within the scope of the present invention and apparent to those of ordinary skill in the art.

[0326] DLBCL

[0327] Disclosed herein, in certain embodiments, is a method for treating a DLBCL in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory DLBCL in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0328] As used herein, the term "Diffuse large B-cell lymphoma (DLBCL)" refers to a neoplasm of the germinal center B lymphocytes with a diffuse growth pattern and a high-intermediate proliferation index. DLBCLs represent approximately 30% of all lymphomas and may present with several morphological variants including the centroblastic, immunoblastic, T-cell/histiocyte rich, anaplastic and plasmoblastic subtypes. Genetic tests have shown that there are different subtypes of DLBCL. These subtypes seem to have different outlooks (prognoses) and responses to treatment. DLBCL can affect any age group but occurs mostly in older people (the average age is mid-60s).

[0329] Disclosed herein, in certain embodiments, is a method for treating diffuse large B-cell lymphoma, activated B cell-like subtype (ABC-DLBCL), in an individual in need thereof, comprising: administering to the individual an irreversible Btk inhibitor in an amount from 300 mg/day up to, and including, 1000 mg/day. The ABC subtype of diffuse large B-cell lymphoma (ABC-DLBCL) is thought to arise from post germinal center B cells that are arrested during plasmatic differentiation. The ABC subtype of DLBCL (ABC-DLBCL) accounts for approximately 30% total DLBCL diagnoses. It is considered the least curable of the DLBCL molecular subtypes and, as such, patients diagnosed with the ABC-DLBCL typically display significantly reduced survival rates compared with individuals with other types of DLBCL. ABC-DLBCL is most commonly associated with chromosomal translocations deregulating the germinal center master regulator BCL6 and with mutations inactivating the PRDM1 gene, which encodes a transcriptional repressor required for plasma cell differentiation.

[0330] A particularly relevant signaling pathway in the pathogenesis of ABC-DLBCL is the one mediated by the nuclear factor (NF)- κ B transcription complex. The NF- κ B family comprises 5 members (p50, p52, p65, c-rel and RelB) that form homo- and heterodimers and function as transcriptional factors to mediate a variety of proliferation, apoptosis, inflammatory and immune responses and are critical for normal B-cell development and survival. NF- κ B is widely used by eukaryotic cells as a regulator of genes that control cell proliferation and cell survival. As such, many different types of human tumors have misregulated NF- κ B: that is, NF- κ B is constitutively active. Active NF- κ B turns on the expression of genes that keep the cell proliferating and protect the cell from conditions that would otherwise cause it to die via apoptosis.

[0331] The dependence of ABC DLBCLs on NF- κ B depends on a signaling pathway upstream of I κ B kinase

comprised of CARD11, BCL10 and MALT1 (the CBM complex). Interference with the CBM pathway extinguishes NF- κ B signaling in ABC DLBCL cells and induces apoptosis. The molecular basis for constitutive activity of the NF- κ B pathway is a subject of current investigation but some somatic alterations to the genome of ABC DLBCLs clearly invoke this pathway. For example, somatic mutations of the coiled-coil domain of CARD11 in DLBCL render this signaling scaffold protein able to spontaneously nucleate protein-protein interaction with MALT1 and BCL10, causing IKK activity and NF- κ B activation. Constitutive activity of the B cell receptor signaling pathway has been implicated in the activation of NF- κ B in ABC DLBCLs with wild type CARD11, and this is associated with mutations within the cytoplasmic tails of the B cell receptor subunits CD79A and CD79B. Oncogenic activating mutations in the signaling adapter MYD88 activate NF- κ B and synergize with B cell receptor signaling in sustaining the survival of ABC DLBCL cells. In addition, inactivating mutations in a negative regulator of the NF- κ B pathway, A20, occur almost exclusively in ABC DLBCL.

[0332] Indeed, genetic alterations affecting multiple components of the NF- κ B signaling pathway have been recently identified in more than 50% of ABC-DLBCL patients, where these lesions promote constitutive NF- κ B activation, thereby contributing to lymphoma growth. These include mutations of CARD11 (~10% of the cases), a lymphocyte-specific cytoplasmic scaffolding protein that—together with MALT1 and BCL10—forms the BCR signalosome, which relays signals from antigen receptors to the downstream mediators of NF- κ B activation. An even larger fraction of cases (~30%) carry biallelic genetic lesions inactivating the negative NF- κ B regulator A20. Further, high levels of expression of NF- κ B target genes have been observed in ABC-DLBCL tumor samples. See, e.g., U. Klein et al., (2008), *Nature Reviews Immunology* 8:22-23; R. E. Davis et al., (2001), *Journal of Experimental Medicine* 194:1861-1874; G. Lentz et al., (2008), *Science* 319:1676-1679; M. Compagno et al., (2009), *Nature* 459:712-721; and L. Srinivasan et al., (2009), *Cell* 139:573-586).

[0333] DLBCL cells of the ABC subtype, such as OCI-Ly10, have chronic active BCR signaling and are very sensitive to the Btk inhibitor described herein. The irreversible Btk inhibitor described herein potently and irreversibly inhibits the growth of OCI-Ly10 (EC₅₀ continuous exposure=10 nM, EC₅₀ 1 hour pulse=50 nM). In addition, induction of apoptosis, as shown by caspase activation, Annexin-V flow cytometry and increase in sub-G0 fraction is observed in OCI-Ly10. Both sensitive and resistant cells express Btk at similar levels, and the active site of Btk is fully occupied by the inhibitor in both as shown using a fluorescently labeled affinity probe. OCI-Ly10 cells are shown to have chronically active BCR signaling to NF- κ B which is dose dependently inhibited by the Btk inhibitors described herein. The activity of Btk inhibitors in the cell lines studied herein are also characterized by comparing signal transduction profiles (Btk, PLC γ , ERK, NF- κ B, AKT), cytokine secretion profiles and mRNA expression profiles, both with and without BCR stimulation, and observed significant differences in these profiles that lead to clinical biomarkers that identify the most sensitive patient populations to Btk inhibitor treatment. See U.S. Pat. No.

7,711,492 and Staudt et al., Nature, Vol. 463, Jan. 7, 2010, pp. 88-92, the contents of which are incorporated by reference in their entirety.

[0334] Follicular Lymphoma

[0335] Disclosed herein, in certain embodiments, is a method for treating a follicular lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory follicular lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0336] As used herein, the term “follicular lymphoma” refers to any of several types of non-Hodgkin’s lymphoma in which the lymphomatous cells are clustered into nodules or follicles. The term follicular is used because the cells tend to grow in a circular, or nodular, pattern in lymph nodes. The average age for people with this lymphoma is about 60.

[0337] CLL/SLL

[0338] Disclosed herein, in certain embodiments, is a method for treating a CLL or SLL in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory CLL or SLL in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0339] Chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) are commonly thought as the same disease with slightly different manifestations. Where the cancerous cells gather determines whether it is called CLL or SLL. When the cancer cells are primarily found in the lymph nodes, lima bean shaped structures of the lymphatic system (a system primarily of tiny vessels found in the body), it is called SLL. SLL accounts for about 5% to 10% of all lymphomas. When most of the cancer cells are in the bloodstream and the bone marrow, it is called CLL.

[0340] Both CLL and SLL are slow-growing diseases, although CLL, which is much more common, tends to grow slower. CLL and SLL are treated the same way. They are usually not considered curable with standard treatments, but depending on the stage and growth rate of the disease, most patients live longer than 10 years. Occasionally over time, these slow-growing lymphomas may transform into a more aggressive type of lymphoma.

[0341] Chronic lymphoid leukemia (CLL) is the most common type of leukemia. It is estimated that 100,760 people in the United States are living with or are in remission from CLL. Most (>75%) people newly diagnosed with CLL are over the age of 50. Currently CLL treatment focuses on controlling the disease and its symptoms rather than on an outright cure. CLL is treated by chemotherapy, radiation therapy, biological therapy, or bone marrow transplantation. Symptoms are sometimes treated surgically (splenectomy removal of enlarged spleen) or by radiation therapy (“de-bulking” swollen lymph nodes). Though CLL progresses slowly in most cases, it is considered generally incurable. Certain CLLs are classified as high-risk. As used herein, “high risk CLL” means CLL characterized by at least one of the following 1) 17p13-; 2) 11q22-; 3) unmutated IgVH together with ZAP-70+ and/or CD38+; or 4) trisomy 12.

[0342] CLL treatment is typically administered when the patient’s clinical symptoms or blood counts indicate that the disease has progressed to a point where it may affect the patient’s quality of life.

[0343] Small lymphocytic leukemia (SLL) is very similar to CLL described supra, and is also a cancer of B-cells. In SLL the abnormal lymphocytes mainly affect the lymph nodes. However, in CLL the abnormal cells mainly affect the blood and the bone marrow. The spleen may be affected in both conditions. SLL accounts for about 1 in 25 of all cases of non-Hodgkin lymphoma. It can occur at any time from young adulthood to old age, but is rare under the age of 50. SLL is considered an indolent lymphoma. This means that the disease progresses very slowly, and patients tend to live many years after diagnosis. However, most patients are diagnosed with advanced disease, and although SLL responds well to a variety of chemotherapy drugs, it is generally considered to be incurable. Although some cancers tend to occur more often in one gender or the other, cases and deaths due to SLL are evenly split between men and women. The average age at the time of diagnosis is 60 years.

[0344] Although SLL is indolent, it is persistently progressive. The usual pattern of this disease is one of high response rates to radiation therapy and/or chemotherapy, with a period of disease remission. This is followed months or years later by an inevitable relapse. Re-treatment leads to a response again, but again the disease will relapse. This means that although the short-term prognosis of SLL is quite good, over time, many patients develop fatal complications of recurrent disease. Considering the age of the individuals typically diagnosed with CLL and SLL, there is a need in the art for a simple and effective treatment of the disease with minimum side-effects that do not impede on the patient’s quality of life. The instant invention fulfills this long standing need in the art.

[0345] Mantle Cell Lymphoma

[0346] Disclosed herein, in certain embodiments, is a method for treating a Mantle cell lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory Mantle cell lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0347] As used herein, the term, “Mantle cell lymphoma” refers to a subtype of B-cell lymphoma, due to CD5 positive antigen-naive pregerminal center B-cell within the mantle zone that surrounds normal germinal center follicles. MCL cells generally over-express cyclin D1 due to a t(11:14) chromosomal translocation in the DNA. More specifically, the translocation is at t(11;14)(q13;q32). Only about 5% of lymphomas are of this type. The cells are small to medium in size. Men are affected most often. The average age of patients is in the early 60s. The lymphoma is usually widespread when it is diagnosed, involving lymph nodes, bone marrow, and, very often, the spleen. Mantle cell lymphoma is not a very fast growing lymphoma, but is difficult to treat.

[0348] Marginal Zone B-Cell Lymphoma

[0349] Disclosed herein, in certain embodiments, is a method for treating a marginal zone B-cell lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating

relapsed or refractory marginal zone B-cell lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0350] As used herein, the term “marginal zone B-cell lymphoma” refers to a group of related B-cell neoplasms that involve the lymphoid tissues in the marginal zone, the patchy area outside the follicular mantle zone. Marginal zone lymphomas account for about 5% to 10% of lymphomas. The cells in these lymphomas look small under the microscope. There are 3 main types of marginal zone lymphomas including extranodal marginal zone B-cell lymphomas, nodal marginal zone B-cell lymphoma, and splenic marginal zone lymphoma.

[0351] MALT

[0352] Disclosed herein, in certain embodiments, is a method for treating a MALT in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory MALT in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0353] The term “mucosa-associated lymphoid tissue (MALT) lymphoma”, as used herein, refers to extranodal manifestations of marginal-zone lymphomas. Most MALT lymphoma are a low grade, although a minority either manifest initially as intermediate-grade non-Hodgkin lymphoma (NHL) or evolve from the low-grade form. Most of the MALT lymphoma occur in the stomach, and roughly 70% of gastric MALT lymphoma are associated with *Helicobacter pylori* infection. Several cytogenetic abnormalities have been identified, the most common being trisomy 3 or t(11;18). Many of these other MALT lymphoma have also been linked to infections with bacteria or viruses. The average age of patients with MALT lymphoma is about 60.

[0354] Nodal Marginal Zone B-Cell Lymphoma

[0355] Disclosed herein, in certain embodiments, is a method for treating a nodal marginal zone B-cell lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory nodal marginal zone B-cell lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0356] The term “nodal marginal zone B-cell lymphoma” refers to an indolent B-cell lymphoma that is found mostly in the lymph nodes. The disease is rare and only accounts for 1% of all Non-Hodgkin’s Lymphomas (NHL). It is most commonly diagnosed in older patients, with women more susceptible than men. The disease is classified as a marginal zone lymphoma because the mutation occurs in the marginal zone of the B-cells. Due to its confinement in the lymph nodes, this disease is also classified as nodal.

[0357] Splenic Marginal Zone B-Cell Lymphoma

[0358] Disclosed herein, in certain embodiments, is a method for treating a splenic marginal zone B-cell lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory splenic marginal zone B-cell

lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0359] The term “splenic marginal zone B-cell lymphoma” refers to specific low-grade small B-cell lymphoma that is incorporated in the World Health Organization classification. Characteristic features are splenomegaly, moderate lymphocytosis with villous morphology, intrasinusoidal pattern of involvement of various organs, especially bone marrow, and relative indolent course. Tumor progression with increase of blastic forms and aggressive behavior are observed in a minority of patients. Molecular and cytogenetic studies have shown heterogeneous results probably because of the lack of standardized diagnostic criteria.

[0360] Burkitt Lymphoma

[0361] Disclosed herein, in certain embodiments, is a method for treating a Burkitt lymphoma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory Burkitt lymphoma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0362] The term “Burkitt lymphoma” refers to a type of Non-Hodgkin Lymphoma (NHL) that commonly affects children. It is a highly aggressive type of B-cell lymphoma that often starts and involves body parts other than lymph nodes. In spite of its fast-growing nature, Burkitt’s lymphoma is often curable with modern intensive therapies. There are two broad types of Burkitt’s lymphoma—the sporadic and the endemic varieties:

[0363] Endemic Burkitt’s lymphoma: The disease involves children much more than adults, and is related to Epstein Barr Virus (EBV) infection in 95% cases. It occurs primarily in equatorial Africa, where about half of all childhood cancers are Burkitt’s lymphoma. It characteristically has a high chance of involving the jawbone, a rather distinctive feature that is rare in sporadic Burkitt’s. It also commonly involves the abdomen.

[0364] Sporadic Burkitt’s lymphoma: The type of Burkitt’s lymphoma that affects the rest of the world, including Europe and the Americas is the sporadic type. Here too, it’s mainly a disease in children. The link between Epstein Barr Virus (EBV) is not as strong as with the endemic variety, though direct evidence of EBV infection is present in one out of five patients. More than the involvement of lymph nodes, it is the abdomen that is notably affected in more than 90% of the children. Bone marrow involvement is more common than in the sporadic variety.

[0365] Waldenstrom Macroglobulinemia

[0366] Disclosed herein, in certain embodiments, is a method for treating a Waldenstrom macroglobulinemia in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory Waldenstrom macroglobulinemia in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0367] The term “Waldenstrom macroglobulinemia”, also known as lymphoplasmacytic lymphoma, is cancer involving a subtype of white blood cells called lymphocytes. It is characterized by an uncontrolled clonal proliferation of terminally differentiated B lymphocytes. It is also charac-

terized by the lymphoma cells making an antibody called immunoglobulin M (IgM). The IgM antibodies circulate in the blood in large amounts, and cause the liquid part of the blood to thicken, like syrup. This can lead to decreased blood flow to many organs, which can cause problems with vision (because of poor circulation in blood vessels in the back of the eyes) and neurological problems (such as headache, dizziness, and confusion) caused by poor blood flow within the brain. Other symptoms can include feeling tired and weak, and a tendency to bleed easily. The underlying etiology is not fully understood but a number of risk factors have been identified, including the locus 6p21.3 on chromosome 6. There is a 2- to 3-fold risk increase of developing WM in people with a personal history of autoimmune diseases with autoantibodies and particularly elevated risks associated with hepatitis, human immunodeficiency virus, and rickettsiosis.

[0368] Multiple Myeloma

[0369] Disclosed herein, in certain embodiments, is a method for treating a myeloma in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory myeloma in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0370] Multiple myeloma, also known as MM, myeloma, plasma cell myeloma, or as Kahler's disease (after Otto Kahler) is a cancer of the white blood cells known as plasma cells. A type of B cell, plasma cells are a crucial part of the immune system responsible for the production of antibodies in humans and other vertebrates. They are produced in the bone marrow and are transported through the lymphatic system.

[0371] Leukemia

[0372] Disclosed herein, in certain embodiments, is a method for treating a leukemia in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. Further disclosed herein, in certain embodiments, is a method for treating relapsed or refractory leukemia in an individual in need thereof, comprising: administering to the individual a therapeutically-effective amount of Compound 1.

[0373] Leukemia is a cancer of the blood or bone marrow characterized by an abnormal increase of blood cells, usually leukocytes (white blood cells). Leukemia is a broad term covering a spectrum of diseases. The first division is between its acute and chronic forms: (i) acute leukemia is characterized by the rapid increase of immature blood cells. This crowding makes the bone marrow unable to produce healthy blood cells. Immediate treatment is required in acute leukemia due to the rapid progression and accumulation of the malignant cells, which then spill over into the bloodstream and spread to other organs of the body. Acute forms of leukemia are the most common forms of leukemia in children; (ii) chronic leukemia is distinguished by the excessive build up of relatively mature, but still abnormal, white blood cells. Typically taking months or years to progress, the cells are produced at a much higher rate than normal cells, resulting in many abnormal white blood cells in the blood. Chronic leukemia mostly occurs in older people, but can theoretically occur in any age group. Additionally, the diseases are subdivided according to which kind of blood cell is affected. This split divides leukemias into lympho-

blastic or lymphocytic leukemias and myeloid or myelogenous leukemias: (i) lymphoblastic or lymphocytic leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes, which are infection-fighting immune system cells; (ii) myeloid or myelogenous leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form red blood cells, some other types of white cells, and platelets.

[0374] Within these main categories, there are several subcategories including, but not limited to, Acute lymphoblastic leukemia (ALL), precursor B-cell acute lymphoblastic leukemia (precursor B-ALL; also called precursor B-lymphoblastic leukemia), Acute myelogenous leukemia (AML), Chronic myelogenous leukemia (CML), and Hairy cell leukemia (HCL). Accordingly, disclosed herein, in certain embodiments, is a method for treating Acute lymphoblastic leukemia (ALL), precursor B-cell acute lymphoblastic leukemia (precursor B-ALL; also called precursor B-lymphoblastic leukemia), Acute myelogenous leukemia (AML), Chronic myelogenous leukemia (CML), or Hairy cell leukemia (HCL) in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. In some embodiments, the leukemia is a relapsed or refractory leukemia. In some embodiments, the leukemia is a relapsed or refractory Acute lymphoblastic leukemia (ALL), relapsed or refractory precursor B-cell acute lymphoblastic leukemia (precursor B-ALL; also called precursor B-lymphoblastic leukemia), relapsed or refractory Acute myelogenous leukemia (AML), relapsed or refractory Chronic myelogenous leukemia (CML), or relapsed or refractory Hairy cell leukemia (HCL).

[0375] Symptoms, diagnostic tests, and prognostic tests for each of the above-mentioned conditions are known. See, e.g., *Harrison's Principles of Internal Medicine*®, 16th ed., 2004, The McGraw-Hill Companies, Inc. Dey et al. (2006), *Cytojournal* 3(24), and the "Revised European American Lymphoma" (REAL) classification system (see, e.g., the website maintained by the National Cancer Institute).

[0376] A number of animal models of are useful for establishing a range of therapeutically effective doses of irreversible Btk inhibitor compounds, such as Compound 1, for treating any of the foregoing diseases.

[0377] The therapeutic efficacy of Compound 1 for any one of the foregoing diseases can be optimized during a course of treatment. For example, a subject being treated can undergo a diagnostic evaluation to correlate the relief of disease symptoms or pathologies to inhibition of in vivo Btk activity achieved by administering a given dose of Compound 1. Cellular assays known in the art can be used to determine in vivo activity of Btk in the presence or absence of an irreversible Btk inhibitor. For example, since activated Btk is phosphorylated at tyrosine 223 (Y223) and tyrosine 551 (Y551), phospho-specific immunocytochemical staining of P-Y223 or P-Y551-positive cells can be used to detect or quantify activation of Btk in a population of cells (e.g., by FACS analysis of stained vs unstained cells). See, e.g., Nisitani et al. (1999), *Proc. Natl. Acad. Sci. USA* 96:2221-2226. Thus, the amount of the Btk inhibitor compound that is administered to a subject can be increased or decreased as needed so as to maintain a level of Btk inhibition optimal for treating the subject's disease state.

[0378] Compound 1 can irreversibly inhibit Btk and may be used to treat mammals suffering from Bruton's tyrosine kinase-dependent or Bruton's tyrosine kinase mediated con-

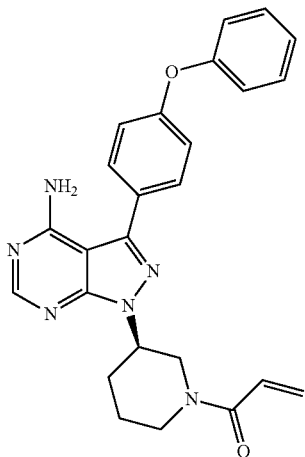
ditions or diseases, including, but not limited to, cancer, autoimmune and other inflammatory diseases. Compound 1 has shown efficacy in a wide variety of diseases and conditions that are described herein.

[0379] In some embodiments, Compound 1 is used for the manufacture of a medicament for treating any of the foregoing conditions (e.g., autoimmune diseases, inflammatory diseases, allergy disorders, B-cell proliferative disorders, or thromboembolic disorders).

Compound 1, and Pharmaceutically Acceptable Salts Thereof

[0380] The Btk inhibitor compound described herein (i.e. Compound 1) is selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk. The Btk inhibitor compound can form a covalent bond with Cys 481 of Btk (e.g., via a Michael reaction).

[0381] “Compound 1” or “1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one” or “1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl)prop-2-en-1-one” or “2-Propen-1-one, 1-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl-” or ibrutinib or any other suitable name refers to the compound with the following structure:



[0382] A wide variety of pharmaceutically acceptable salts is formed from Compound 1 and includes:

[0383] acid addition salts formed by reacting Compound 1 with an organic acid, which includes aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanic acids, hydroxyl alkanic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, amino acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like;

[0384] acid addition salts formed by reacting Compound 1 with an inorganic acid, which includes hydro-

chloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like.

[0385] The term “pharmaceutically acceptable salts” in reference to Compound 1 refers to a salt of Compound 1, which does not cause significant irritation to a mammal to which it is administered and does not substantially abrogate the biological activity and properties of the compound.

[0386] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms (solvates). Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of product formation or isolation with pharmaceutically acceptable solvents such as water, ethanol, methanol, methyl tert-butyl ether (MTBE), diisopropyl ether (DIPE), ethyl acetate, isopropyl acetate, isopropyl alcohol, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), acetone, nitromethane, tetrahydrofuran (THF), dichloromethane (DCM), dioxane, heptanes, toluene, anisole, acetonitrile, and the like. In one aspect, solvates are formed using, but not limited to, Class 3 solvent(s). Categories of solvents are defined in, for example, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), “Impurities: Guidelines for Residual Solvents, Q3C (R3), (November 2005). Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of Compound 1, or pharmaceutically acceptable salts thereof, are conveniently prepared or formed during the processes described herein. In some embodiments, solvates of Compound 1 are anhydrous. In some embodiments, Compound 1, or pharmaceutically acceptable salts thereof, exist in unsolvated form. In some embodiments, Compound 1, or pharmaceutically acceptable salts thereof, exist in unsolvated form and are anhydrous.

[0387] In yet other embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, is prepared in various forms, including but not limited to, amorphous phase, crystalline forms, milled forms and nano-particulate forms. In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, is amorphous. In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, is amorphous and anhydrous. In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, is amorphous. In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, is amorphous and anhydrous.

[0388] In some embodiments, Compound 1 is prepared as outlined in U.S. Pat. No. 7,514,444.

Amorphous Compound 1

[0389] In some embodiments, Compound 1 is amorphous and anhydrous. In some embodiments, Compound 1 is amorphous. In some embodiments, Compound 1 is amorphous and in spray-dried form.

[0390] Preparation of SD Forms

[0391] In some embodiments, spray-dried forms of ibrutinib are prepared as outlined in the Examples. It is noted that solvents, temperatures and other reaction conditions presented herein may vary.

Dosage Forms

[0392] The pharmaceutical compositions described herein can be formulated for administration to a mammal via any conventional means including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, or intramuscular), buccal, intranasal, rectal or transdermal administration routes. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0393] Moreover, the pharmaceutical compositions described herein, which include Compound 1 can be formulated into any suitable dosage form, including but not limited to, solid oral dosage forms, controlled release formulations, fast melt formulations, effervescent formulations, tablets, powders, pills, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[0394] Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[0395] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[0396] In some embodiments, the solid dosage forms disclosed herein may be in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder) a capsule (including both soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or "sprinkle capsules"), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including but not limited to, a fast-melt tablet. Additionally, pharmaceutical formulations described herein may be administered as a

single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, or three, or four, capsules or tablets.

[0397] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of Compound 1 with one or more pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the particles of Compound 1 are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also include film coatings, which disintegrate upon oral ingestion or upon contact with diluent. These formulations can be manufactured by conventional pharmacological techniques.

[0398] Conventional pharmacological techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. See, e.g., Lachman et al., *The Theory and Practice of Industrial Pharmacy* (1986). Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[0399] The pharmaceutical solid dosage forms described herein can include Compound 1 and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000), a film coating is provided around the formulation of Compound 1. In one embodiment, some or all of the particles of the Compound 1 are coated. In another embodiment, some or all of the particles of the Compound 1 are microencapsulated. In still another embodiment, the particles of the Compound 1 are not microencapsulated and are uncoated.

[0400] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[0401] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[0402] In order to release the Compound 1 from a solid dosage form matrix as efficiently as possible, disintegrants

are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like. In some embodiments provided herein, the disintegrating agent is selected from the group consisting of natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, cross-linked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch such as sodium starch glycolate, cross-linked polymer such as crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, or a gum. In some embodiments provided herein, the disintegrating agent is croscarmellose sodium.

[0403] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose (e.g. Hypromellose USP Pharmacopoeia 603, hydroxypropylmethylcellulose acetate stearate (Aquate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®), ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®), microcrystalline dextrose, amylose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA), crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitab®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[0404] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies whether direct compres-

sion, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder. Formulators skilled in art can determine the binder level for the formulations, but binder usage level of up to 70% in tablet formulations is common.

[0405] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glyceryl behenate, glyceryl palmitostearate, glyceryl benzoate, magnesium or sodium lauryl sulfate, and the like. In some embodiments provided herein, the lubricant is selected from the group consisting of stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, stearic acid, sodium stearates, magnesium stearate, zinc stearate, and waxes. In some embodiments provided herein, the lubricant is magnesium stearate.

[0406] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrans and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like. In some embodiments provided herein, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrans, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, microcrystalline cellulose, microcellulose, and talc. In some embodiments provided herein, the diluent is microcrystalline cellulose.

[0407] The term “non water-soluble diluent” represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified starches and microcrystalline cellulose, and microcellulose (e.g., having a density of about 0.45 g/cm³, e.g. Avicel, powdered cellulose), and talc.

[0408] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, quaternary ammonium compounds (e.g., Polyquat 10®), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like.

[0409] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, poloxamers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like. In some embodiments provided herein, the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, poloxamers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide. In some embodiments provided herein, the surfactant is sodium lauryl sulfate.

[0410] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to,

polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulose, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[0411] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[0412] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

[0413] In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearyl, stearate, and castor oil.

[0414] Compressed tablets are solid dosage forms prepared by compacting the bulk blend of the formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will include one or more flavoring agents. In other embodiments, the compressed tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of Compound 1 from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings including Opadry® typically range from about 1% to about 3% of the tablet weight. In other embodiments, the compressed tablets include one or more excipients.

[0415] A capsule may be prepared, for example, by placing the bulk blend of the formulation of Compound 1 inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments, the therapeutic dose is split into mul-

tle (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the formulation is delivered in a capsule form.

[0416] In various embodiments, the particles of Compound 1 and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

[0417] In another aspect, dosage forms may include microencapsulated formulations. In some embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not limited to, pH modifiers, erosion facilitators, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[0418] Materials useful for the microencapsulation described herein include materials compatible with Compound 1 which sufficiently isolate the Compound 1 from other non-compatible excipients. Materials compatible with Compound 1 are those that delay the release of the compounds of Compound 1 in vivo.

[0419] Exemplary microencapsulation materials useful for delaying the release of the formulations including compounds described herein, include, but are not limited to, hydroxypropyl cellulose ethers (HPC) such as Klucel® or Nisso HPC, low-substituted hydroxypropyl cellulose ethers (L-HPC), hydroxypropyl methyl cellulose ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Methocel®-E, Opadry YS, PrimaFlo, Benecel MP824, and Benecel MP843, methylcellulose polymers such as Methocel®-A, hydroxypropylmethylcellulose acetate Aqoat (HF-LS, HF-LG, HF-MS) and Metolose®, Ethylcelluloses (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®, Polyvinyl alcohol (PVA) such as Opadry AMB, hydroxyethylcelluloses such as Natrosol®, carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC, polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®, monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D, Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, Eudragit® NE30D, and Eudragit® NE 40D, cellulose acetate phthalate, sepiifilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials.

[0420] In still other embodiments, plasticizers such as polyethylene glycols, e.g., PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for delaying the release of the pharmaceutical compositions is from the USP or the National Formulary (NF). In yet other embodiments, the

microencapsulation material is Klucel. In still other embodiments, the microencapsulation material is methocel.

[0421] Microencapsulated Compound 1 may be formulated by methods known by one of ordinary skill in the art. Such known methods include, e.g., spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, e.g., complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ polymerization, in-liquid drying, and desolvation in liquid media could also be used. Furthermore, other methods such as roller compaction, extrusion/spheronization, coacervation, or nanoparticle coating may also be used.

[0422] In one embodiment, the particles of Compound 1 are microencapsulated prior to being formulated into one of the above forms. In still another embodiment, some or most of the particles are coated prior to being further formulated by using standard coating procedures, such as those described in *Remington's Pharmaceutical Sciences*, 20th Edition (2000).

[0423] In other embodiments, the solid dosage formulations of the Compound 1 are plasticized (coated) with one or more layers. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearyl, stearate, and castor oil.

[0424] In other embodiments, a powder including the formulations with Compound 1 may be formulated to include one or more pharmaceutical excipients and flavors. Such a powder may be prepared, for example, by mixing the formulation and optional pharmaceutical excipients to form a bulk blend composition. Additional embodiments also include a suspending agent and/or a wetting agent. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units.

[0425] In still other embodiments, effervescent powders are also prepared in accordance with the present disclosure. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When salts of the compositions described herein are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing "effervescence." Examples of effervescent salts include, e.g., the following ingredients: sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use and result in a pH of about 6.0 or higher.

[0426] In some embodiments, the solid dosage forms described herein can be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which uti-

lizes an enteric coating to affect release in the small intestine of the gastrointestinal tract. The enteric coated dosage form may be a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. The enteric coated oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

[0427] The term "delayed release" as used herein refers to the delivery so that the release can be accomplished at some generally predictable location in the intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. In some embodiments the method for delay of release is coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the methods and compositions described herein to achieve delivery to the lower gastrointestinal tract. In some embodiments the polymers described herein are anionic carboxylic polymers. In other embodiments, the polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to:

[0428] Shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH>7;

[0429] Acrylic polymers. The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonium methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine;

[0430] Cellulose Derivatives. Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH>6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP pseudolatex with particles <1 μm . Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethylcellulose acetate succinate include, but are not limited to, AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dis-

solves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions; Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH>5, and it is much less permeable to water vapor and gastric fluids.

[0431] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflex A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[0432] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[0433] In other embodiments, the formulations described herein, which include Compound 1 are delivered using a pulsatile dosage form. A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Many other types of controlled release systems known to those of ordinary skill in the art and are suitable for use with the formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, plyphanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman et al., *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh et al., *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725, 4,624,848, 4,968,509, 5,461,140, 5,456,923, 5,516,527, 5,622,721, 5,686,105, 5,700,410, 5,977,175, 6,465,014 and 6,932,983, each of which is specifically incorporated by reference.

[0434] In some embodiments, pharmaceutical formulations are provided that include particles of Compound 1 at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[0435] It is to be appreciated that there is overlap between the above-listed additives used in the aqueous dispersions or suspensions described herein, since a given additive is often classified differently by different practitioners in the field, or is commonly used for any of several different functions. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in formulations described herein. The

amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

Dosing and Treatment Regimens

[0436] In some embodiments, the amount of Compound 1 that is administered to a mammal is from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of Compound 1 that is administered to a mammal is from 420 mg/day up to, and including, 840 mg/day. In some embodiments, the amount of Compound 1 that is administered to a mammal is about 420 mg/day, or about 560 mg/day, or about 840 mg/day. In some embodiments, the amount of Compound 1 that is administered to a mammal is about 420 mg/day. In some embodiments, the amount of Compound 1 that is administered to a mammal is about 560 mg/day. In some embodiments, the AUC₀₋₂₄ of Compound 1 is between about 150 and about 3500 ng*h/mL. In some embodiments, the AUC₀₋₂₄ of Compound 1 is between about 500 and about 1100 ng*h/mL. In some embodiments, Compound 1 is administered orally. In some embodiments, Compound 1 is administered once per day, twice per day, or three times per day. In some embodiments, Compound 1 is administered daily. In some embodiments, Compound 1 is administered once daily. In some embodiments, Compound 1 is administered every other day. In some embodiments, the Compound 1 is a maintenance therapy.

[0437] Compound 1 can be used in the preparation of medicaments for the inhibition of Btk or a homolog thereof, or for the treatment of diseases or conditions that would benefit, at least in part, from inhibition of Btk or a homolog thereof, including a subject diagnosed with a hematological malignancy. In addition, a method for treating any of the diseases or conditions described herein in a subject in need of such treatment, involves administration of pharmaceutical compositions containing Compound 1, or a pharmaceutically acceptable salt, pharmaceutically acceptable N-oxide, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said subject.

[0438] The compositions containing Compound 1 can be administered for prophylactic, therapeutic, or maintenance treatment. In some embodiments, compositions containing Compound 1 are administered for therapeutic applications (e.g., administered to a subject diagnosed with a hematological malignancy). In some embodiments, compositions containing Compound 1 are administered for therapeutic applications (e.g., administered to a subject susceptible to or otherwise at risk of developing a hematological malignancy). In some embodiments, compositions containing Compound 1 are administered to a patient who is in remission as a maintenance therapy.

[0439] Amounts of Compound 1 will depend on the use (e.g., therapeutic, prophylactic, or maintenance). Amounts of Compound 1 will depend on severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. It is considered well within the skill of the art for one to determine such therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial). In some embodiments, the amount of Compound 1 is from 300 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of Compound 1 is from 420 mg/day up

to, and including, 840 mg/day. In some embodiments, the amount of Compound 1 is from 400 mg/day up to, and including, 860 mg/day. In some embodiments, the amount of Compound 1 is about 360 mg/day. In some embodiments, the amount of Compound 1 is about 420 mg/day. In some embodiments, the amount of Compound 1 is about 560 mg/day. In some embodiments, the amount of Compound 1 is about 840 mg/day. In some embodiments, the amount of Compound 1 is from 2 mg/kg/day up to, and including, 13 mg/kg/day. In some embodiments, the amount of Compound 1 is from 2.5 mg/kg/day up to, and including, 8 mg/kg/day. In some embodiments, the amount of Compound 1 is from 2.5 mg/kg/day up to, and including, 6 mg/kg/day. In some embodiments, the amount of Compound 1 is from 2.5 mg/kg/day up to, and including, 4 mg/kg/day. In some embodiments, the amount of Compound 1 is about 2.5 mg/kg/day. In some embodiments, the amount of Compound 1 is about 8 mg/kg/day.

[0440] In some embodiments, pharmaceutical compositions described herein include about 140 mg of Compound 1. In some embodiments, a capsule formulation is prepared that includes about 140 mg of Compound 1. In some embodiments, 2, 3, 4, or 5 of the capsule formulations are administered daily. In some embodiments, 3 or 4 of the capsules are administered daily. In some embodiments, 3 of the 140 mg capsules are administered once daily. In some embodiments, 4 of the 140 mg capsules are administered once daily. In some embodiments, the capsules are administered once daily. In other embodiments, the capsules are administered multiple times a day.

[0441] In some embodiments, Compound 1 is administered daily. In some embodiments, Compound 1 is administered every other day.

[0442] In some embodiments, Compound 1 is administered once per day. In some embodiments, Compound 1 is administered twice per day. In some embodiments, Compound 1 is administered three times per day. In some embodiments, Compound 1 is administered four times per day.

[0443] In some embodiments, Compound 1 is administered until disease progression, unacceptable toxicity, or individual choice. In some embodiments, Compound 1 is administered daily until disease progression, unacceptable toxicity, or individual choice. In some embodiments, Compound 1 is administered every other day until disease progression, unacceptable toxicity, or individual choice.

[0444] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously; alternatively, the dose of drug being administered may be temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). The length of the drug holiday can vary between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday may be from 10%-100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%.

[0445] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration,

or both, can be reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[0446] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, the severity of the disease, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, and the subject or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, or from about 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0447] The pharmaceutical composition described herein may be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. The unit dosage may be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers can be used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection may be presented in unit dosage form, which include, but are not limited to ampoules, or in multi-dose containers, with an added preservative. In some embodiments, each unit dosage form comprises 140 mg of Compound 1. In some embodiments, an individual is administered 1 unit dosage form per day. In some embodiments, an individual is administered 2 unit dosage forms per day. In some embodiments, an individual is administered 3 unit dosage forms per day. In some embodiments, an individual is administered 4 unit dosage forms per day.

[0448] The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages may be altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[0449] Toxicity and therapeutic efficacy of such therapeutic regimens can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between LD₅₀ and ED₅₀. Compounds exhibiting high therapeutic indices are preferred. The data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in human. The dosage of such compounds

lies preferably within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

Combination Therapy

[0450] In certain instances, it is appropriate to administer Compound 1 in combination with another therapeutic agent.

[0451] In one embodiment, the compositions and methods described herein are also used in conjunction with other therapeutic reagents that are selected for their particular usefulness against the condition that is being treated. In general, the compositions described herein and, in embodiments where combinational therapy is employed, other agents do not have to be administered in the same pharmaceutical composition, and are, because of different physical and chemical characteristics, administered by different routes. In one embodiment, the initial administration is made according to established protocols, and then, based upon the observed effects, the dosage, modes of administration and times of administration, further modified.

[0452] In various embodiments, the compounds are administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the disease, the condition of the patient, and the actual choice of compounds used. In certain embodiments, the determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is based upon evaluation of the disease being treated and the condition of the patient.

[0453] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth.

[0454] The individual compounds of such combinations are administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. In one embodiment, the individual compounds will be administered simultaneously in a combined pharmaceutical formulation. Appropriate doses of known therapeutic agents will be appreciated by those skilled in the art.

[0455] The combinations referred to herein are conveniently presented for use in the form of a pharmaceutical compositions together with a pharmaceutically acceptable diluent(s) or carrier(s).

[0456] Disclosed herein, in certain embodiments, is a method for treating a cancer in an individual in need thereof, comprising: administering to the individual an amount of Compound 1. In some embodiments, the method further comprises administering a second cancer treatment regimen.

[0457] In some embodiments, administering a Btk inhibitor before a second cancer treatment regimen reduces immune-mediated reactions to the second cancer treatment regimen. In some embodiments, administering Compound 1 before ofatumumab reduces immune-mediated reactions to ofatumumab.

[0458] In some embodiments, the second cancer treatment regimen comprises a chemotherapeutic agent, a steroid, an immunotherapeutic agent, a targeted therapy, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises a B cell receptor pathway inhibitor. In some embodiments, the B cell receptor pathway

inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLC γ inhibitor, a PKC β inhibitor, or a combination thereof. In some embodiments, the second cancer treatment regimen comprises an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, an immunotherapy, a radioimmunotherapeutic, a DNA damaging agent, a proteasome inhibitor, a Cyp3A4 inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

[0459] In some embodiments, the second cancer treatment regimen comprises chlorambucil, ifosfamide, doxorubicin, mesalazine, thalidomide, lenalidomide, temsirolimus, everolimus, fludarabine, fostamatinib, paclitaxel, docetaxel, ofatumumab, rituximab, dexamethasone, prednisone, CAL-101, ibritumomab, tositumomab, bortezomib, carfilzomib, pentostatin, endostatin, EPOCH-R, DA-EPOCH-R, rifampin, selinexor, gemcitabine, obinutuzumab, carmustine, cytarabine, melphalan, ublituximab, palbociclib, ACP-196 (Acerta Pharma BV), TGR-1202 (TG Therapeutics, Inc.), TEDDI, TEDD, MEDI4736 (AstraZeneca), ABT-0199 (AbbVie), CC-122 (Celgene Corporation), LD-AraC, ketoconazole, etoposide, carboplatin, moxifloxacin, citrovorum, methotrexate, filgrastim, mesna, vincristine, cyclophosphamide, erythromycin, voriconazole, nivolumab or a combination thereof.

[0460] In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone, and optionally, rituximab.

[0461] In some embodiments, the second cancer treatment regimen comprises bendamustine, and rituximab.

[0462] In some embodiments, the second cancer treatment regimen comprises fludarabine, cyclophosphamide, and rituximab.

[0463] In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone, and optionally, rituximab.

[0464] In some embodiments, the second cancer treatment regimen comprises etoposide, doxorubicin, vinristine, cyclophosphamide, prednisolone, and optionally, rituximab.

[0465] In some embodiments, the second cancer treatment regimen comprises dexamethasone and lenalidomide.

[0466] In some embodiments, the second cancer treatment regimen comprises a proteasome inhibitor. In some embodiments, the second treatment comprises bortezomib. In some embodiments, the second cancer treatment comprises an epoxyketone. In some embodiments, the second cancer treatment comprises epoxomicin. In some embodiments, the second cancer treatment comprises a tetrapeptide epoxyketone. In some embodiments, the second cancer treatment comprises carfilzomib. In some embodiments, the second cancer treatment comprises disulfiram, epigallocatechin-3-gallate, salinosporamide A, ONX 0912, CEP-18770, MLN9708, or MG132.

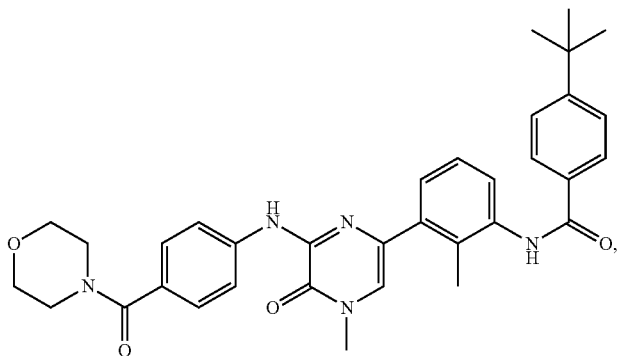
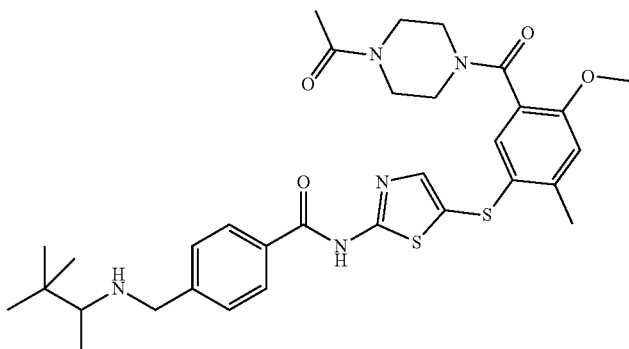
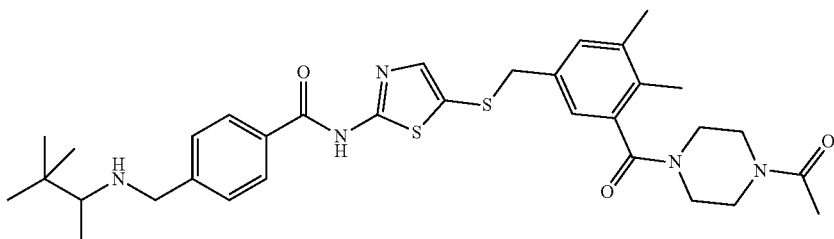
[0467] In some embodiments, the second cancer treatment regimen comprises a Cyp3A4 inhibitor. In some embodiments, the second cancer treatment regimen comprises indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone. In some embodiments, the second cancer treatment regimen comprises ketoconazole.

[0468] In some embodiments, the second cancer treatment comprises a Janus Kinase (JAK) inhibitor. In some embodiments, the second treatment comprises Lestaurtinib, Tofacitinib, Ruxolitinib, CYT387, Baricitinib or Pacritinib.

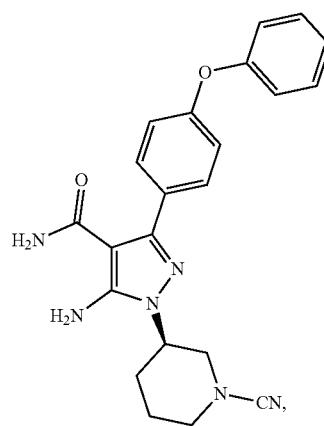
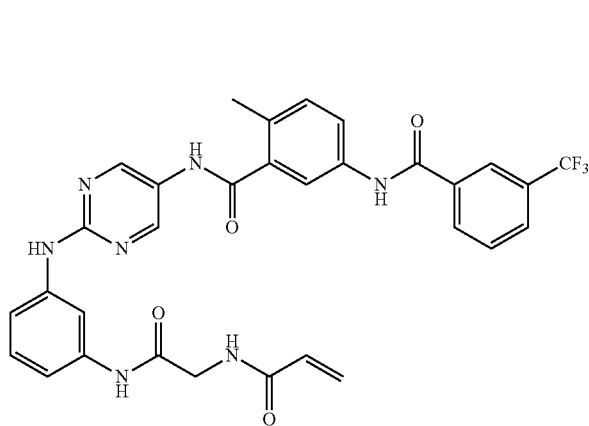
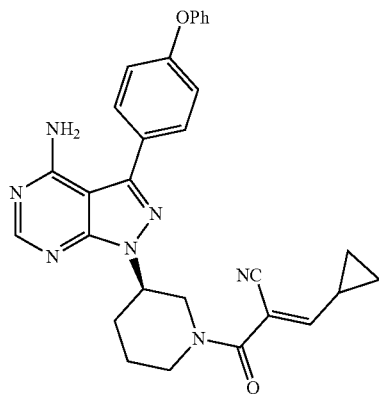
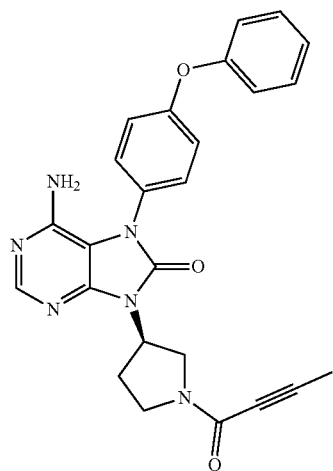
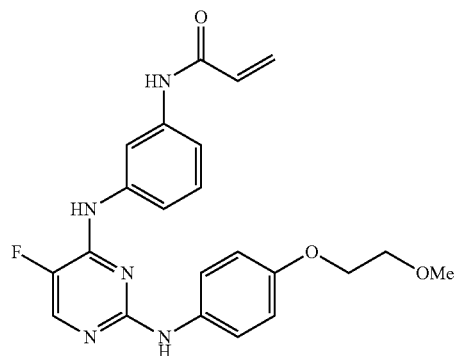
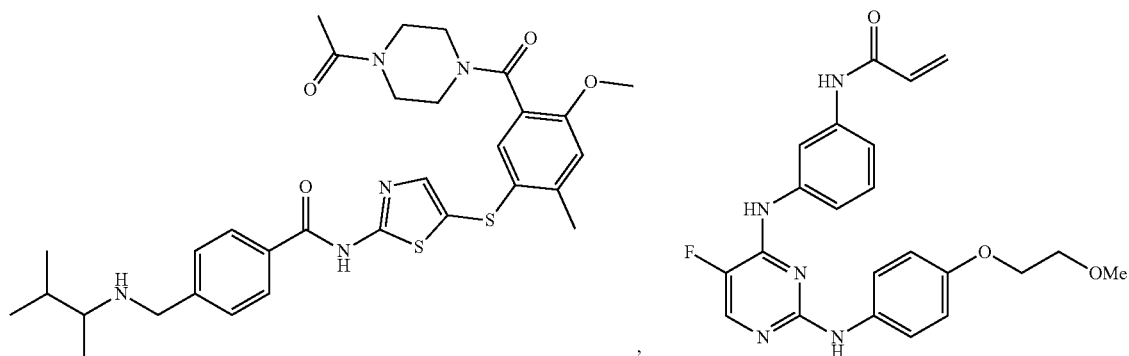
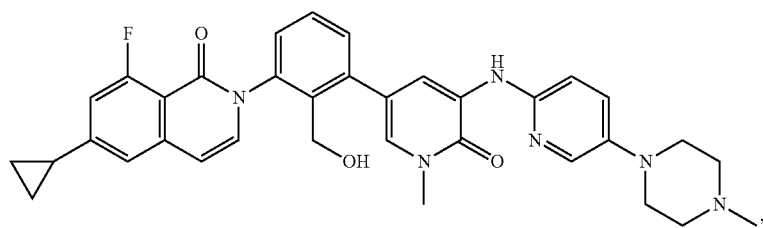
[0469] In some embodiments, the second cancer treatment comprises a histone deacetylase inhibitor (HDAC inhibitor, HDI). In some embodiments, the second cancer treatment comprises a hydroxamic acid (or hydroxamate), such as trichostatin A, vorinostat (SAHA), belinostat (PXD101), LAQ824, and panobinostat (LBH589), a cyclic tetrapeptide, such as trapoxin B, a depsipeptide, a benzamide, such as entinostat (MS-275), CI994, and mocetinostat (MGCD0103), an electrophilic ketone, or an aliphatic acid compound, such as phenylbutyrate and valproic acid.

[0470] In some embodiments, the second cancer treatment comprises a BTK inhibitor. In some embodiments, the Btk inhibitor is AVL-263 (Avila Therapeutics/Celgene Corporation), AVL-292 (Avila Therapeutics/Celgene Corporation), AVL-291 (Avila Therapeutics/Celgene Corporation), BMS-488516 (Bristol-Myers Squibb), BMS-509744 (Bristol-Myers Squibb), CGI-1746 (CGI Pharma/Gilead Sciences), CTA-056, GDC-0834 (Genentech), GDC-0853 (Genentech), HY-11066 (also, CTK417891, HMS3265G21,

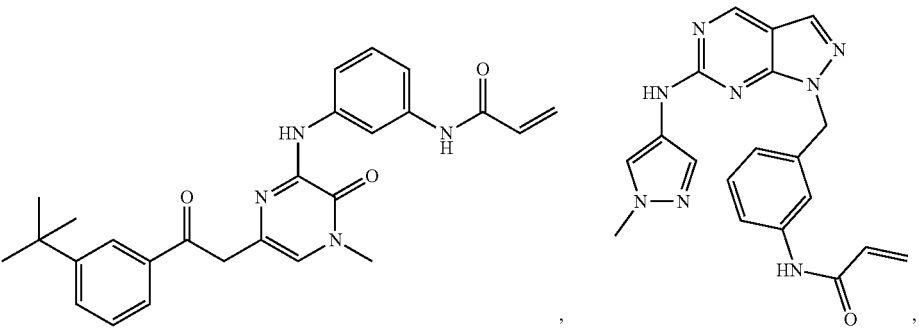
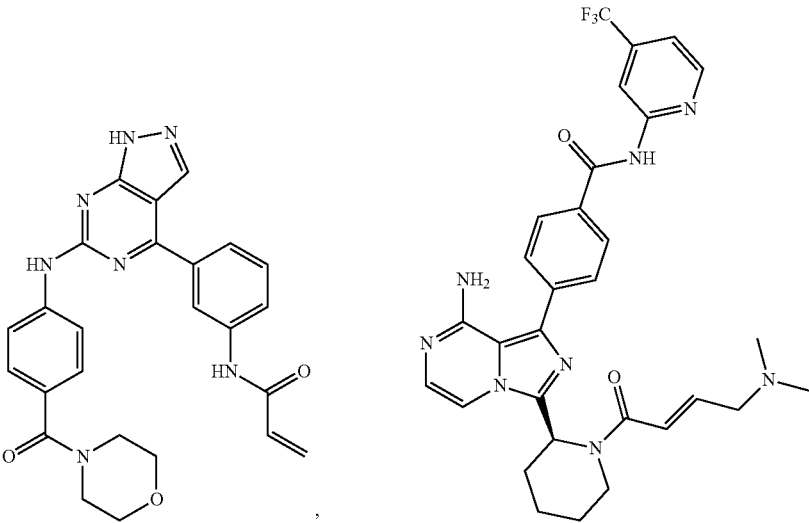
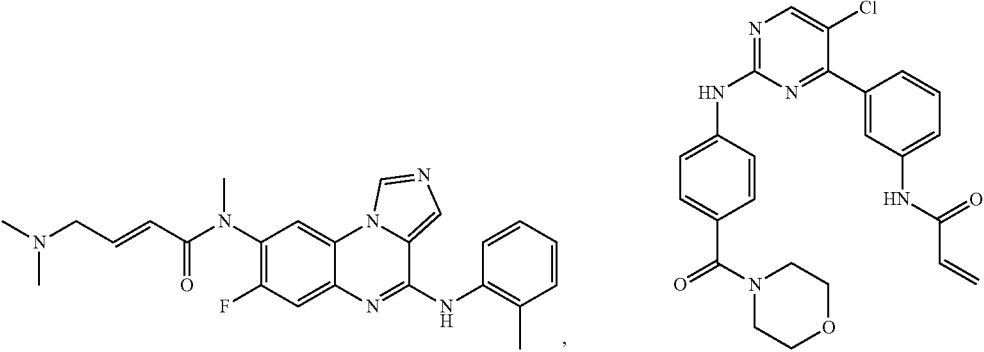
HMS3265G22, HMS3265H21, HMS3265H22, 439574-61-5, AG-F-54930), ONO-4059 (Ono Pharmaceutical Co., Ltd.), ONO-WG37 (Ono Pharmaceutical Co., Ltd.), PLS-123 (Peking University), RN486 (Hoffmann-La Roche), or HM71224 (Hanmi Pharmaceutical Company Limited). In some embodiments, the Btk inhibitor is 4-(tert-butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide (CGI-1746); 7-benzyl-1-(3-(piperidin-1-yl)propyl)-2-(4-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (CTA-056); (R)-N-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (GDC-0834); 6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-2H-isoquinolin-1-one (RN-486); N-[5-[5-(4-acetylpiperazine-1-carbonyl-methoxy-2-methylphenyl)sulfanyl-1,3-thiazol-2-yl]-4-[(3,3-dimethylbutan-2-ylamino)methyl]benzamide (BMS-509744, HY-11092); or N-(5-((5-(4-Acetylpiperazine-1-carbonyl)-4-methoxy-2-methylphenyl)thio)thiazol-2-yl)-4-(((3-methylbutan-2-yl)amino)methyl)benzamide (HY11066). In some embodiments, the Btk inhibitor is:



-continued



-continued



cin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pirarubicin, valrubicin, zorubicin; Other Cytotoxic Antibiotics such as for example bleomycin, ixabepilone, mitomycin, plicamycin; Platinum Compounds such as for example carboplatin, cisplatin, oxaliplatin, satraplatin; Methylhydrazines such as for example procarbazine; Sensitizers such as for example aminolevulinic acid, efaproxiral, methyl aminolevulinate, porfimer sodium, temoporfin; Protein Kinase Inhibitors such as for example dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, temsirolimus; Other Antineoplastic Agents such as for example alitretinoin, altretamine, amzacrone, anagrelide, arsenic trioxide, asparaginase, bexarotene, bortezomib, celecoxib, denileukin diftitox, estramustine, hydroxycarbamide, irinotecan, lonidamine, masoprocol, miltefosine, mitoguanzone, mitotane, oblimersen, pegaspargase, pentostatin, romidepsin, sitimagene ceradenovec, tiazofurine, topotecan, tretinoin, vorinostat; Estrogens such as for example diethylstilbenol, ethinylestradiol, fosfestrol, polyestradiol phosphate; Progestogens such as for example gestonorone, medroxyprogesterone, megestrol; Gonadotropin Releasing Hormone Analogs such as for example busserelin, goserelin, leuporelin, triptorelin; Anti-Estrogens such as for example fulvestrant, tamoxifen, toremifene; Anti-Androgens such as for example bicalutamide, flutamide, nilutamide, Enzyme Inhibitors, aminoglutethimide, anastrozole, exemestane, formestane, letrozole, vorozole; Other Hormone Antagonists such as for example abarelix, degarelix; Immunostimulants such as for example histamine dihydrochloride, mifamurtide, pidotimod, plerixafor, roquinimex, thymopentin; Immunosuppressants such as for example everolimus, gusperimus, leflunomide, mycophenolic acid, sirolimus; Calcineurin Inhibitors such as for example ciclosporin, tacrolimus; Other Immunosuppressants such as for example azathioprine, lenalidomide, methotrexate, thalidomide; and Radiopharmaceuticals such as for example, iobenguane.

[0472] Additional cancer treatment regimens include interferons, interleukins, Tumor Necrosis Factors, Growth Factors, or the like.

[0473] Additional cancer treatment regimens include Immunostimulants such as for example ancestim, filgrastim, lenograstim, molgramostim, pegfilgrastim, sargramostim; Interferons such as for example interferon alfa natural, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-n1, interferon beta natural, interferon beta-1a, interferon beta-1b, interferon gamma, peginterferon alfa-2a, peginterferon alfa-2b; Interleukins such as for example aldesleukin, oprelvekin; Other Immunostimulants such as for example BCG vaccine, glatiramer acetate, histamine dihydrochloride, immunocyanin, lentinan, melanoma vaccine, mifamurtide, pegademase, pidotimod, plerixafor, poly I:C, poly ICLC, roquinimex, tasonermin, thymopentin; Immunosuppressants such as for example abatacept, abetimus, alefacept, antilymphocyte immunoglobulin (horse), antithymocyte immunoglobulin (rabbit), eculizumab, efalizumab, everolimus, gusperimus, leflunomide, muromab-CD3, mycophenolic acid, natalizumab, sirolimus; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, etanercept, golimumab, infliximab; Interleukin Inhibitors such as for example anakinra, basiliximab, canakinumab, daclizumab, mepolizumab, riloncept, tocilizumab, ustekinumab; Calcineurin Inhibitors such as for example ciclosporin, tacrolimus; Other Immu-

nosuppressants such as for example azathioprine, lenalidomide, methotrexate, thalidomide.

[0474] Additional cancer treatment regimens include Adalimumab, Alemtuzumab, Basiliximab, Bevacizumab, Cetuximab, Certolizumab pegol, Daclizumab, Eculizumab, Efalizumab, Gemtuzumab, Ibritumomab tiuxetan, Infliximab, Muromonab-CD3, Natalizumab, Panitumumab, Ranibizumab, Rituximab, Tositumomab, Trastuzumab, or the like, or a combination thereof.

[0475] Additional cancer treatment regimens include Monoclonal Antibodies such as for example alemtuzumab, bevacizumab, catumaxomab, cetuximab, edrecolomab, gemtuzumab, ofatumumab, panitumumab, rituximab, trastuzumab, Immunosuppressants, eculizumab, efalizumab, muromab-CD3, natalizumab; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, golimumab, infliximab, Interleukin Inhibitors, basiliximab, canakinumab, daclizumab, mepolizumab, tocilizumab, ustekinumab, Radiopharmaceuticals, ibritumomab tiuxetan, tositumomab; Others Monoclonal Antibodies such as for example abagovomab, adecatumumab, alemtuzumab, anti-CD30 monoclonal antibody Xmab2513, anti-MET monoclonal antibody MetMab, apolizumab, apomab, arcitumomab, basiliximab, bispecific antibody 2B1, blinatumomab, brentuximab vedotin, capromab pendetide, cixutumumab, claudiximab, conatumumab, dacetuzumab, denosumab, eculizumab, epratuzumab, epratuzumab, ertumaxomab, etaracizumab, figitumumab, fresolimumab, galiximab, ganitumab, gemtuzumab ozogamicin, glembatumumab, ibritumomab, inotuzumab ozogamicin, ipilimumab, lexatumumab, lintuzumab, lintuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, monoclonal antibody CC49, necitumumab, nimotuzumab, ofatumumab, oregovomab, pertuzumab, ramacurimab, ranibizumab, siplizumab, sonpizumab, tanezumab, tositumomab, trastuzumab, tremelimumab, tucotuzumab celmoleukin, veltuzumab, visilizumab, volociximab, zalutumumab.

[0476] Additional cancer treatment regimens include agents that affect the tumor micro-environment such as cellular signaling network (e.g. phosphatidylinositol 3-kinase (PI3K) signaling pathway, signaling from the B-cell receptor and the IgE receptor). In some embodiments, the second agent is a PI3K signaling inhibitor or a syc kinase inhibitor. In one embodiment, the syk inhibitor is R788. In another embodiment is a PKC γ inhibitor such as by way of example only, enzastaurin.

[0477] Examples of agents that affect the tumor micro-environment include PI3K signaling inhibitor, syc kinase inhibitor, Protein Kinase Inhibitors such as for example dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, temsirolimus; Other Angiogenesis Inhibitors such as for example GT-111, JI-101, R1530; Other Kinase Inhibitors such as for example AC220, AC480, ACE-041, AMG 900, AP24534, Any-614, AT7519, AT9283, AV-951, axitinib, AZD1152, AZD7762, AZD8055, AZD8931, bafetinib, BAY 73-4506, BGJ398, BGT226, BI 811283, BI6727, BIBF 1120, BIBW 2992, BMS-690154, BMS-777607, BMS-863233, BSK-461364, CAL-101, CEP-11981, CYC116, DCC-2036, dinaciclib, dovitinib lactate, E7050, EMD 1214063, ENMD-2076, fostamatinib disodium, GSK2256098, GSK690693, INCB18424, INNO-406, JNJ-26483327, JX-594, KX2-391, linifanib, LY2603618, MGCD265, MK-0457, MK1496, MLN8054, MLN8237, MP470, NMS-1116354, NMS-

1286937, ON 01919.Na, OSI-027, OSI-930, Btk inhibitor, PF-00562271, PF-02341066, PF-03814735, PF-04217903, PF-04554878, PF-04691502, PF-3758309, PHA-739358, PLC3397, progenipointin, R547, R763, ramucirumab, regorafenib, R05185426, SAR103168, SCH 727965, SGI-1176, SGX523, SNS-314, TAK-593, TAK-901, TKI258, TLN-232, TTP607, XL147, XL228, XL281RO5126766, XL418, XL765.

[0478] Further examples of anti-cancer agents for use in combination with a Btk inhibitor compound include inhibitors of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan).

[0479] Other anti-cancer agents that can be employed in combination with a Btk inhibitor compound include Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; broprimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexamaplatin; dezaguanine; dezaguanine mesylate; diaziqone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1 a; interferon gamma-1 b; iroplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; roglitimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur;

teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazoferin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride.

[0480] Other anti-cancer agents that can be employed in combination with a Btk inhibitor compound include: 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; purinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; beta-clamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-aminotriazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatin; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziqone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; iimofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-such as for example growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron;

jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombicine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannosatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullin; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogetimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine;

thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topostatin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; typhostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vaporeotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

[0481] Yet other anticancer agents that can be employed in combination with a Btk inhibitor compound include alkylating agents, antimetabolites, natural products, or hormones, e.g., nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, etc.), or triazines (decarbazine, etc.). Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[0482] Examples of alkylating agents that can be employed in combination a Btk inhibitor compound include, but are not limited to, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitne, semustine, streptozocin, etc.), or triazines (decarbazine, etc.). Examples of antimetabolites include, but are not limited to folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin).

[0483] Examples of anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules and which can be used in combination with a Btk inhibitor compound include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Sobliodotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Dai-ichi), FR-182877 (Fujisawa, also known as WS-9885B),

GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCI), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCI, and RPR-258062A), Vitilevuamide, Tubulylin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyeleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeside, Caribaolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

[0484] Where the individual is suffering from or at risk of suffering from an autoimmune disease, an inflammatory disease, or an allergy disease, Compound 1 can be used in with one or more of the following therapeutic agents in any combination: immunosuppressants (e.g., tacrolimus, cyclosporin, rapamicin, methotrexate, cyclophosphamide, azathioprine, mercaptopurine, mycophenolate, or FTY720), glucocorticoids (e.g., prednisone, cortisone acetate, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, beclometasone, fludrocortisone acetate, deoxycorticosterone acetate, aldosterone), non-steroidal anti-inflammatory drugs (e.g., salicylates, arylalkanoic acids, 2-arylpropionic acids, N-arylanthranilic acids, oxicams, coxibs, or sulphonanilides), Cox-2-specific inhibitors (e.g., valdecoxib, celecoxib, or rofecoxib), leflunomide, gold thioglucose, gold thiomalate, aurofin, sulfasalazine, hydroxychloroquine, minocycline, TNF- α binding proteins (e.g., infliximab, etanercept, or adalimumab), abatacept, anakinra, interferon- β , interferon- γ , interleukin-2, allergy vaccines, antihistamines, antileukotrienes, beta-agonists, theophylline, or anticholinergics.

Kits/Articles of Manufacture

[0485] For use in the therapeutic methods of use described herein, kits and articles of manufacture are also described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[0486] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, e.g., U.S. Pat. No. 5,323,907. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[0487] In some embodiments, the compounds or compositions described herein, are presented in a package or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The compound or composition described herein is packaged alone, or packaged with another compound or another ingredient or additive. In some embodiments, the package contains one or more containers filled with one or more of the ingredients of the pharmaceutical compositions. In some embodiments, the package comprises metal or plastic foil, such as a blister pack. In some embodiments, the package or dispenser device is accompanied by instructions for administration, such as instructions for administering the compounds or compositions for treating a neoplastic disease. In some embodiments, the package or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. In some embodiments, such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions include a compound described herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0488] For example, the container(s) include Compound 1, optionally in a composition or in combination with another agent as disclosed herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[0489] A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[0490] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific

therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[0491] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

[0492] The following ingredients, formulations, processes and procedures for practicing the methods disclosed herein correspond to that described above.

Example 1: Preparation of Spray-Dried Forms of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (ibrutinib) (Compound 1)

[0493] The spray dry mixture solvent was prepared by solubilizing both ibrutinib and a polymer in acetone at a total solid weight concentration of 10%. The mixture was thoroughly mixed until completely dissolved to avoid solid clumps during spraying. Acetone was selected as solvent for spray drying because it provided adequate ibrutinib and polymer solubility and was more favorable solvent than other solvents considered. Ibrutinib solid weight of 2% or 5% with 8% or 5% polymer solvent mixtures were spray dried at 15 ml/min speed with a nozzle size of 1.5 mm and nozzle pressure at 20 psi. The inlet temperature was set between 70 to 80° C., and the outlet temperature was set between 40 to 45° C. The drying gas flow was maintained at 35 m³/hr. Secondary drying was performed at 40° C. in an oven for about 16 hours to further reduce moisture or acetone from the solid dispersed powder. Spray drying runs yielded from 80 to 90% with no material significant accumulation on the spray dry chamber across a wide range of spray-drying conditions and/or different solvent mixtures during screening phase.

TABLE 1

Examples of Spray Dried (SD) Compositions Comprising Ibrutinib		
SD Composition	Components	Ratio
b	Ibrutinib:Soluplus®	1:1
c	Ibrutinib:HPMCAS-M	1:1
d	Ibrutinib:HPMCAS-M	1:4
e	Ibrutinib:PVP-VA	1:2
f	Ibrutinib:PVP-VA:soluplus	1:1:1
g	Ibrutinib:PVP-VA	1:1

Example 2: Chiral Purity Determination

[0494] Chiral purity of Compound 1 was determined by using a Lux Cellulose-1 chiral column by normal phase HPLC. The mobile phase is composed of 20% isopropyl alcohol and 80% hexanes. The enantiomers of 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one are detected at 260 nm. In one embodiment, Compound 1 is dissolved in a mixture of Hexanes: IPA=(7:3) to obtain a concentration of approximately 0.2 mg/mL and the chiral purity of the sample is analyzed. The content of the R enantiomer is determined by peak area normalization of the enantiomer peaks and is expressed in weight to weight percent. In some embodiments, a sample of Compound 1 includes less than 5.0%, less than 4.0%, less than 3.0%, less than 2.0%, or less than 1.0%, of the (S)-isomer. In some embodiments, a sample of Compound 1 includes less than 1.0% of the (S)-isomer.

Example 3: Formulation A (Capsule)

[0495] In one embodiment, capsule formulations of Compound 1 for administration to humans are prepared with the following ingredients:

TABLE 2

Formulation A		
Excipient or Active		% (w/w)
API	Ibrutinib	42.42
Diluent	Microcrystalline cellulose	45.88
Surfactant	Sodium Lauryl Sulfate	4.25
Disintegrant	Croscarmellose sodium	6.97
Lubricant	Magnesium Stearate	0.48
Capsule	Gelatin	—

[0496] In some embodiments, the manufacturing process includes the following steps: i) weigh the indicated amount of the components, ii) mix together, iii) granulate the mixture, (iii) prepare final blend by adding additional disintegrant, surfactant and lubricant (iv) fill the final blend into an appropriate size capsule, (v) close the capsule. In some embodiments, the capsules are stored at room temperature for an extended period of time until they are used.

Example 4: Formulation B (SD with Soluplus®)

[0497] Ibrutinib with Soluplus solid dispersion intermediate (50% active spray-dried ibrutinib) was blended with lactose, microcrystalline cellulose, croscarmellose, silicon dioxide and 0.25% of magnesium stearate in a V-blender for 10 minutes. The blend mixture was then screened through a size 20 mesh. Additional magnesium stearate of 0.25% was added to the post-screened blend and blended additionally for 3 minutes. The final blend was roller compacted to obtain a ribbon or slug using a roller compactor or a single press station. Compacted ribbons or slugs were milled using a mill granulator and screened through a size 20 mesh before compressing into tablets using a single station tablet press.

TABLE 3

Formulation B		
Excipient		% (w/w)
Spray Dried API*	Ibrutinib	25.00
Spray Dried Polymer*	Soluplus®	25.00

TABLE 3-continued

Formulation B		
Excipient		% (w/w)
Diluent 1	Lactose	17.00
Diluent 2	Microcrystalline cellulose	25.50
Disintegrant	Croscarmellose sodium	6.00
Glidant	Colloidal Silicon Dioxide	1.00
Lubricant	Magnesium Stearate	0.50

*50% active spray-dried ibrutinib

Example 5: Formulation C (SD with HPMCAS-M)

[0498] Ibrutinib with HPMCAS-M solid dispersion intermediate (50% active spray-dried ibrutinib) was blended with lactose, microcrystalline cellulose, croscarmellose, silicon dioxide and 0.25% of magnesium stearate in a V-blender for 10 minutes. The blend mixture was then screened through a size 20 mesh. Additional magnesium stearate of 0.25% was added to the post-screened blend and blended additionally for 3 minutes. The final blend was roller compacted to obtain a ribbon or slug using a roller compactor or a single press station. Compacted ribbons or slugs were milled using a mill granulator and screened through a size 20 mesh before compressing into tablets using a single station tablet press.

TABLE 4

Formulation C		
Excipient		% (w/w)
Spray Dried API*	Ibrutinib	26.925
Spray Dried Polymer*	HPMCAS-M	26.925
Diluent 1	Lactose	14.00
Diluent 2	Microcrystalline cellulose	24.65
Disintegrant	Croscarmellose sodium	6.00
Glidant	Colloidal Silicon Dioxide	1.00
Lubricant	Magnesium Stearate	0.50

*50% active spray-dried ibrutinib

Example 6: Formulation D (SD with HPMCAS-M)

[0499] Ibrutinib with HPMCAS-M solid dispersion intermediate (20% active spray-dried ibrutinib) was blended with lactose, microcrystalline cellulose, croscarmellose, silicon dioxide and 0.25% of magnesium stearate in a V-blender for 10 minutes. The blend mixture was then screened through a size 20 mesh. Additional magnesium stearate of 0.25% was added to the post-screened blend and blended additionally for 3 minutes. The final blend was roller compacted to obtain a ribbon or slug using a roller compactor or a single press station. Compacted ribbons or slugs were milled using a mill granulator and screened through a size 20 mesh before compressing into tablets using a single station tablet press.

TABLE 5

Formulation D		
Excipient		% (w/w)
Spray Dried API*	Ibrutinib	10.77
Spray Dried Polymer*	HPMCAS-M	43.08
Diluent 1	Lactose	14.00
Diluent 2	Microcrystalline cellulose	24.65

TABLE 5-continued

Formulation D		
Excipient		% (w/w)
Disintegrant	Croscarmellose sodium	6.00
Glidant	Colloidal Silicon Dioxide	1.00
Lubricant	Magnesium Stearate	0.50

*20% active spray-dried ibrutinib

Example 6: Tablet Formulations E, F and G (SD with Polyvinylpyrrolidone/Vinyl Acetate (PVP-VA) Co-Polymer and Optional Soluplus)

[0500]

TABLE 6

Tablet Formulations E and F				
		(mg)		
Component	% w/w	Formulation E	Formulation F	
Spray Dried Ibrutinib	46.67	140	140	
Composition PVP-VA		280	140	
		0	140	
Prosolv® EasyTab*	22.83	205.47	205.47	
Sodium Stearyl Fumarate	0.25	2.25	2.25	
Intragranular Total	69.75	627.72	627.72	
Crospovidone/Kollidon CL F	30.00	270.00	270.00	
Sodium Stearyl Fumarate	0.25	2.25	2.25	
Extragranular Total	30.25	272.25	272.25	
Total	100.00	899.97	899.97	

*Prosolv® EasyTab (JRS PHARMA LP, USA) is an excipient composite comprising a binder-filler, glidant, disintegrant, and lubricant, in particular, microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate, and sodium stearyl fumarate.

TABLE 7

Tablet Formulation G			
Component		% w/w	mg
Spray Dried Ibrutinib		31.11	140
Composition PVP-VA			140
Prosolv® EasyTab		22.83	205.47
Sodium Stearyl Fumarate		0.25	2.25
Intragranular Total		54.19	487.72
Extra-Granular Polymer Soluplus		15.56	140
Crospovidone/Kollidon CL F		30.00	270.00
Sodium Stearyl Fumarate		0.25	2.25
Extragranular Total		45.81	412.25
Total		100.00	899.97

Example 7: Immediate Release Tablets

[0501] In some embodiments, tablets are prepared with the components set forth in Table 8.

TABLE 8

Components of Tablet Formulation	
Ingredient	Range
Spray-dried ibrutinib	5% to 50%
Hypromellose	2% to 10%

TABLE 8-continued

Components of Tablet Formulation	
Ingredient	Range
Croscarmellose sodium	0% to 15%
Microcrystalline cellulose	5% to 50%
Lactose	10% to 75%
Magnesium stearate	0.25% to 2.5%
Total	Tablet weight range: 300 mg to 1000 mg

Example 8: Immediate Release Tablets

[0502] In some embodiments, tablets are prepared with the components set forth in Table 9.

TABLE 9

Components of Tablet Formulation			
Component	Tested Excipient	Tested % w/w	Propose Range % w/w
Spray Dried API	Ibrutinib	10 to 25	1 to 65
Spray Dried Polymer	HPMCAS & Soluplus	25 to 40	4 to 65
Diluent 1	Lactose	14 to 17	0 to 80
Diluent 2	Microcrystalline cellulose	25	0 to 80
Disintegrant	Croscarmellose sodium	6	3 to 10
Glidant	Colloidal Silicon Dioxide	1	0 to 2
Lubricant	Magnesium Stearate	0.25 to 0.5	0 to 1

[0503] Manufacturing process will typically be granulation (dry, wet or melt) or direct compression.

Example 9: PK Study of Compound 1 in Different Formulations

[0504] In vivo experiments were conducted to evaluate the potential benefit of the solid dispersion formulations relative to conventional formulations such as capsule formulation.

[0505] Particularly, the pharmacokinetics of ibrutinib in capsule (Formulation A) versus different solid dispersion formulations (Formulations B, C, and D) was studied in fasted male beagle dogs following single oral administration of 140 mg ibrutinib formulations administered in a Latin square crossover design. FIG. 1 shows mean plasma concentration-time profiles of ibrutinib following single oral dose administration of different ibrutinib formulations to fasted beagle dogs (Dose=140 mg). In general, all the solid dispersion formulations tested showed higher concentrations than the capsule formulation A. Specifically, solid dispersion formulations C and D showed on average 9- to 10-fold higher exposure than seen with the capsule formulation (Table 10).

[0506] Furthermore, the solid dispersion formulations of ibrutinib with HPMCAS-M (Formulations C and D) showed about 16-18 fold increase in C_{max} , and about 9-10 fold increase in AUC. Pharmacokinetics of solid dispersion formulations E, F and G were evaluated in pentagastrin treated fasted male beagle dogs following single oral administration of 140 mg ibrutinib in comparison to capsule (Formulation

A). Pretreatment with pentagastrin decreases dog gastric pH to (1-3) similar to human gastric pH and can be used to predict performance in humans. In pentagastrin pretreated dogs, solid dispersion formulations (E, F and G) showed approximately 2- to 3-fold increase in exposure (FIG. 2) and significantly reduced variability in exposure (Table 10).

[0507] Additionally, reduced variability in ibrutinib exposure (both C_{max} and AUC) was consistently observed with solid dispersion formulations C-G when compared to capsule formulation (Table 10).

TABLE 10

Mean (% CV) Ibrutinib Plasma PK Parameters Following Single Dose Administration of Different Ibrutinib Formulations to Fasted Beagle Dogs (n = 7)					
Formulation	C_{max}^{**} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (ng * h/mL)	F_{rel} (%)
A (Capsule)	49.7 (77.0)	2.14	3.92 (92.9)	216 (87.0)	N/A
B	128 (202)	5.00	1.49 (ND)	378 (155)	235 (164)
C	551 (56.0)	1.00	2.52 (95.1)	1321 (45.0)	875 (65.0)
D	799 (67.0)	2.00	2.70 (54.3)	1674 (55.0)	1014 (60.0)
E	783 (39)	0.929	3.21	1394 (49)	227
F	636 (32)	1.00	4.52	1340 (49)	235
G	784 (33)	0.929	2.44	1488 (41)	261

Frel: $(AUC_{FormulationB,C \text{ or } D}/AUC_{FormulationA}) * 100$

**coefficient of variation (CV) values are given in parenthesis

N/A: not applicable;

ND: not determined

[0508] In summary, the solid dispersion formulations of ibrutinib comprising the spray-dried form of ibrutinib proved to be advantageous over the capsule formulations.

Example 10: Drug Dissolution

[0509] In-vitro dissolution test for ibrutinib solid dispersion tablets or capsules were performed with 900 ml of 0.05M phosphate buffer at pH 6.8 with 3% (w/v) polysorbate 20 using USP <711> apparatus 2. The paddle speed was at 75 rpm from 0 to 60 minutes and increased to 250 rpm from 60 to 75 minutes. Samples are filtered at time of collection and analyzed using isocratic reversed-phase high performance liquid chromatography (HPLC) with ultraviolet (UV) detection per Pharmacocyclics method.

[0510] FIG. 3 shows the improved dissolution of the solid dispersion tablet (Formulations C and D) over the dissolution of the capsule formulation (Formulation A). FIG. 4 illustrates the dissolution of the solid dispersion tablet Formulations E, F and G as compared to the capsule formulation (Formulation A).

Example 11: Safety and Tolerability Study of Compound 1 in Chronic Lymphocytic Leukemia

[0511] Purpose: The purpose of this study is to establish the safety and optimal dose of orally administered Compound 1 (420 mg/day) in patients with B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma/diffuse well-differentiated lymphocytic lymphoma.

[0512] Primary Outcome Measures: Safety and tolerability of Compound 1 (frequency, severity, and relatedness of adverse events).

[0513] Secondary Outcome Measures: Pharmacokinetic/Pharmacodynamic assessments. Tumor response—overall

response rate as defined by recent guidelines on CLL and SLL (B cell lymphoma) and duration of response.

[0514] Eligibility: 18 Years and older; both genders are eligible.

[0515] Inclusion Criteria: 1. For treatment-naïve group only: Men and women ≥ 65 years of age with confirmed diagnosis of CLL/SLL, who require treatment per NCI or International Working Group guidelines 11-14. 2. For relapsed/refractory group only: Men and women ≥ 18 years of age with a confirmed diagnosis of relapsed/refractory CLL/SLL unresponsive to therapy (ie, failed ≥ 2 previous treatments for CLL/SLL and at least 1 regimen had to have had a purine analog [eg, fludarabine] for subjects with CLL). 3. Body weight ≥ 40 kg. 4. ECOG performance status of ≤ 2 . 5. Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children. 6. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. 7. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

[0516] Exclusion Criteria: 1. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Compound 1 PO, or put the study outcomes at undue risk. 2. Any immunotherapy, chemotherapy, radiotherapy, or experimental therapy within 4 weeks before first dose of study drug (corticosteroids for disease-related symptoms allowed but require 1-week washout before study drug administration). 3. Central nervous system (CNS) involvement by lymphoma. 4. Major surgery within 4 weeks before first dose of study drug. 5. Creatinine $>1.5 \times$ institutional upper limit of normal (ULN); total bilirubin $>1.5 \times$ ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>2.5 \times$ ULN unless disease related. 6. Concomitant use of medicines known to cause QT prolongation or torsades de pointes. 7. Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc >470 msec. 8. Lactating or pregnant.

Example 12: Safety and Efficacy of Compound 1 in Subjects with Relapsed/Refractory Mantle Cell Lymphoma (MCL)

[0517] The primary objective of this trial is to evaluate the efficacy of Compound 1 in relapsed/refractory subjects with Mantle Cell Lymphoma (MCL). The secondary objective is to evaluate the safety of a fixed daily dosing regimen of Compound 1 (560 mg/day in the form of capsules) in this population.

[0518] Primary Outcome Measures: To Measure the Number of Participants with a Response to Compound 1.

[0519] Secondary Outcome Measures: To measure the number of participants with adverse events as a measure of safety and tolerability. To measure pharmacokinetics to assist in determining how the body responds to the study drug. Patient reported outcomes (to measure the number of participants reported outcomes in determining the health related quality of life).

[0520] Eligibility: 18 Years and older; both genders are eligible.

[0521] Inclusion Criteria: Men and women ≥ 18 years of age. ECOG performance status of ≤ 2 . Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14), and measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions. Documented failure to achieve at least partial response (PR) with, or documented disease progression disease after, the most recent treatment regimen. At least 1, but no more than 5, prior treatment regimens for MCL (Note: Subjects having received ≥ 2 cycles of prior treatment with bortezomib, either as a single agent or as part of a combination therapy regimen, will be considered to be bortezomib-exposed.). Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

[0522] Major exclusion criteria: Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of study drug. Any life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Compound 1 capsules, or put the study outcomes at undue risk. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. Any of the following laboratory abnormalities: 1. Absolute neutrophil count (ANC) <750 cells/mm³ ($0.75 \times 10^9/L$) unless there is documented bone marrow involvement. 2. Platelet count $<50,000$ cells/mm³ ($50 \times 10^9/L$) independent of transfusion support unless there is documented bone marrow involvement. 3. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) $\geq 3.0 \times$ upper limit of normal (ULN). 4. Creatinine $>2.0 \times$ ULN.

Example 13: Phase 2 Study of the Combination of Compound 1 and Rituximab in High-Risk Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma Patients

[0523] Purpose: The goal of this clinical research study is to learn if Compound 1 combined with rituximab can help to control chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The safety of this combination will also be studied.

[0524] Rituximab (375 mg/m²) given intravenously (IV) on Day 1, Day 8, Day 15, and Day 22, then continued once every 4 weeks only on Days 1 during cycles 2-6. Compound 1 started on Day 2 of cycle 1 at a dose of 420 mg (3 \times 140-mg capsules) orally daily and will be continued daily.

[0525] Primary Outcome Measures: Progression free survival (PFS) [Time Frame: 3 months]-progression free survival defined as the time interval from treatment to progressive disease or death, whichever happens earlier. Patients in complete remission (CR), partial remission (PR) or stable disease (SD) are all counted as progression-free. Survival or times to progression functions estimated using the Kaplan-Meier method.

[0526] Secondary Outcome Measures: Toxicity [Time Frame: 3 months]—toxicity reported by type, frequency and severity. Worst toxicity grades per patient tabulated for selected adverse events and laboratory measurements. Toxicity (grade 3 or 4) monitored based on the Bayesian model (beta-binomial) by assuming a priori probability of toxicity following beta(1,1).

[0527] Eligibility: 18 Years and older; both genders are eligible.

[0528] Inclusion Criteria: 1. Patients must have a diagnosis of high-risk CLL/SLL and be previously treated with up to 3 lines of prior therapy. High-risk CLL and high-risk SLL is defined by the presence of a 17p deletion or 11q deletion or TP53 mutation. Any CLL and SLL patient who has a short remission duration of less than 3 years after prior first-line chemo-immunotherapy, such as the FCR regimen, also fulfills criteria of high-risk CLL/SLL, regardless of the presence or absence of cytogenetic abnormalities. 2. CLL and SLL patients with 17p deletion or TP53 mutation will not be required to have received any prior therapy, given the poor outcome of CLL/SLL patients to standard frontline chemo-immunotherapy, such patients will be eligible if they are untreated or if they have received up to 3 lines of prior therapy. 3. Patients must have an indication for treatment by 2008 IWCLL Criteria. 4. Patients age >18 years at the time of signing informed consent. Understand and voluntarily sign an informed consent. Be able to comply with study procedures and follow-up examinations. 5. ECOG/WHO performance status of 0-1. 6. Patients of childbearing potential must be willing to practice highly effective birth control (e.g., condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the study and for 30 days after the last dose of study drug. Women of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal. Post menopause is defined as follows: Amenorrhea ≥ 12 consecutive months without another cause and a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL; a male of childbearing potential is any male that has not been surgically sterilized. 7. Adequate renal and hepatic function as indicated by all of the following: Total bilirubin $\leq 1.5 \times$ institutional Upper Limit of Normal (ULN) except for patients with bilirubin elevation due to Gilbert's disease who will be allowed to participate; an ALT $\leq 2.5 \times$ ULN; and an estimated creatinine clearance (CrCl) of >30 mL/min, as calculated by the Cockcroft-Gault equation unless disease related. 8. Free of prior malignancies for 3 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix or breast. 9. A urine pregnancy test (within 7 days of Day 1) is required for women with childbearing potential

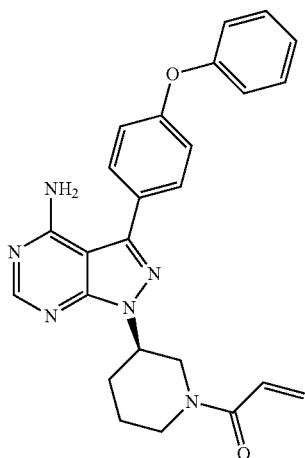
[0529] Exclusion Criteria: 1. Pregnant or breast-feeding females. 2. Treatment including chemotherapy, chemo-im-

munotherapy, monoclonal antibody therapy, radiotherapy, high-dose corticosteroid therapy (more than 60 mg Prednisone or equivalent daily), or immunotherapy within 21 days prior to enrollment or concurrent with this trial. 3. Investigational agent received within 30 days prior to the first dose of study drug or have previously taken Compound 1. If received any investigational agent prior to this time point, drug-related toxicities must have recovered to Grade 1 or less prior to first dose of study drug. 4. Systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment). 5. Patients with uncontrolled Autoimmune Hemolytic Anemia (AIHA) or autoimmune thrombocytopenia (ITP). 6. Patients with severe hematopoietic insufficiency, as defined by an absolute neutrophil count of less than 500/micro-L and/or a platelet count of less than 30,000/micro-L at time of screening for this protocol. 7. Any other severe concurrent disease, or have a history of serious organ dysfunction or disease involving the heart, kidney, liver or other organ system that may place the patient at undue risk to undergo therapy with Compound 1 and rituximab. 8. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. 9. Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc >470 msec. 10. Any serious medical condition, laboratory abnormality, or psychiatric illness that places the subject at unacceptable risk if he/she were to participate in the study. 11. History of stroke or cerebral hemorrhage within 6 months. 12. Evidence of bleeding diathesis or coagulopathy. 13. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1, anticipation of need for major surgical procedure during the course of the study. 14. Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1. Bone marrow aspiration and/or biopsy are allowed. 15. Serious, non-healing wound, ulcer, or bone fracture. 16. Treatment with Coumadin. Patients who recently received Coumadin must be off Coumadin for at least 7 days prior to start of the study. 17. Any chemotherapy (e.g., bendamustine, cyclophosphamide, pentostatin, or fludarabine), immunotherapy (e.g., alemtuzumab, or ofatumumab), bone marrow transplant, experimental therapy, or radiotherapy is prohibited during therapy on this study. 18. Use of medications known to prolong QTc interval or that may be associated with Torsades de Pointes (refer to Appendix F) are prohibited within 7 days of starting study drug and during study-drug treatment.

[0530] The examples and embodiments described herein are illustrative and various modifications or changes suggested to persons skilled in the art are to be included within this disclosure. As will be appreciated by those skilled in the art, the specific components listed in the above examples may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, and the like.

What is claimed is:

1. A solid dispersion pharmaceutical composition comprising solid dispersed ibrutinib, wherein ibrutinib is a compound of formula (I),



(I)

2. The pharmaceutical composition of claim 1, wherein the solid dispersed ibrutinib is a spray-dried ibrutinib composition.

3. The pharmaceutical composition of claim 2, wherein the spray-dried ibrutinib composition comprises ibrutinib dispersed into one or more solubility enhancers.

4. The pharmaceutical composition of claim 3, wherein the solubility enhancer is a polymer matrix; and the polymer matrix comprises one or more polymers.

5. The pharmaceutical composition of claim 4, wherein the spray-dried ibrutinib composition comprises 1-90% w/w ibrutinib dispersed into the polymer matrix.

6. The pharmaceutical composition claim 4, wherein the polymer in the polymer matrix is a linear polymer, a cross-linked polymer, a co-polymer, a graft polymer; or any combination thereof.

7. The pharmaceutical composition of claim 4, wherein the polymer has a molecular weight in a range of about 2,000 to about 500,000 daltons, about 100,000 to about 200,000 daltons, about 200,000 to about 300,000 daltons, or about 400,000 to about 500,000 daltons.

8. A solid dispersion formulation comprising a solid dispersion pharmaceutical composition according to claim 1, and a pharmaceutically acceptable carrier.

9. The solid dispersion formulation of claim 8, wherein the solid dispersion formulation is in a form of a liquid formulation or a solid formulation.

10. The solid dispersion formulation of claim 9, wherein the solid dispersion formulation is in a form of a powder, dry powder, or a lyophilized powder.

11. A solid dispersion formulation comprising a solid dispersion pharmaceutical composition according to claim 1, and one or more excipients.

12. The solid dispersion formulation of claim 11, wherein the excipient comprises present in an amount from about 10 to about 50% w/w.

13. The solid dispersion formulation of claim 11, wherein the formulation comprises lactose, microcrystalline cellulose, and croscarmellose sodium; and

lactose is present in an amount from about 5 to about 20%, about 10 to about 20%, or about 14 to about 19% w/w; microcrystalline cellulose is present in an amount from about 20 to about 30%, about 23 to about 28%, or about 24 to about 26% w/w; and

croscarmellose sodium is present in an amount from about 3 to about 9%, about 4 to about 8%, or about 5 to about 7% w/w.

14. The solid dispersion formulation of claim 11, wherein the formulation further comprises one or more glidants.

15. The solid dispersion formulation of claim 11, wherein the formulation further comprises one or more lubricants.

16. The solid dispersion formulation of claim 15, wherein the lubricant is magnesium stearate; and magnesium stearate is present in an amount from about 0.1 to about 0.5%, or about 0.2 to about 0.3% w/w.

17. The solid dispersion formulation of claim 11, wherein the formulation comprises

a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,

b) about 16 to about 18% w/w of lactose,

c) about 24 to about 26% w/w of microcrystalline cellulose,

d) about 5 to about 7% w/w of croscarmellose sodium,

e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

f) about 0.2 to about 0.8% w/w of magnesium stearate; and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

18. The solid dispersion formulation of claim 11, wherein the formulation comprises

a) about 52 to about 54% w/w of 20% active spray-dried ibrutinib,

b) about 13 to about 15% w/w of lactose,

c) about 24 to about 26% w/w of microcrystalline cellulose,

d) about 5 to about 7% w/w of croscarmellose sodium,

e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

f) about 0.4 to about 0.6% w/w of magnesium stearate; and wherein the 20% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 20% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is hydroxypropyl methyl cellulose acetate succinate (HPMCAS).

19. The solid dispersion formulation of claim 11, wherein the formulation comprises

a) about 49 to about 51% w/w of 50% active spray-dried ibrutinib,

b) about 16 to about 18% w/w of lactose,

c) about 24 to about 26% w/w of microcrystalline cellulose,

d) about 5 to about 7% w/w of croscarmellose sodium,

e) about 0.8 to about 1.2% w/w of colloidal silicon dioxide, and

f) about 0.2 to about 0.8% w/w of magnesium stearate; and wherein the 50% active spray-dried ibrutinib is a spray-dried ibrutinib composition comprising about 50% w/w of ibrutinib dispersed into a polymer matrix; and the polymer in the polymer matrix is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®).

20. A method of treating a disease in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of the pharmaceutical composition of claim 1.

21. A method for treating a cancer comprising administering to a patient in need thereof a therapeutically effective amount of the pharmaceutical composition of claim 1.

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