PHARMACEUTICAL FORMULATIONS OF A BRUTON'S TYROSINE KINASE INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/127,717, filed March 3, 2015, and U.S. Provisional Application No. 62/193,518, filed July 16, 2015, 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, including pharmaceutical compositions, solvates and pharmaceutically acceptable salts thereof, as well as pharmaceutical formulations that include the Btk inhibitor and methods of using the Btk inhibitor compositions or formulations 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 (FcepsilonRI) 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-{(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one or 2-Propen-1-one, 1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-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.

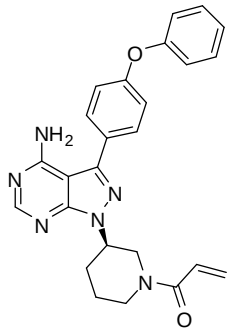
SUMMARY

[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, including pharmaceutically acceptable compositions, formulations, and methods of uses thereof. Also described are pharmaceutically acceptable compositions and formulations of 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, 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. Further described are pharmaceutical compositions and formulations of 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, 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).

[0007] Also described herein is a process for preparing a pharmaceutical composition 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 by a wet granulation method. Further described are pharmaceutical formulations that include a pharmaceutical composition 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 prepared by a wet granulation method.

[0008] Described herein is a pharmaceutical composition comprising ibrutinib, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the pharmaceutical composition comprises at least 50% w/w of ibrutinib.

[0009] In another example described herein is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 50% w/w to about 90% w/w of ibrutinib. In another example described herein is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 50% w/w to about 80% w/w of ibrutinib. In another example described herein is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 60% w/w to about 80% w/w of ibrutinib. In another example described herein is a pharmaceutical composition comprising ibrutinib, wherein the pharmaceutical composition comprises about 60% w/w to about 75% w/w of ibrutinib. In another example described herein is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, wherein the pharmaceutical composition comprises intragranular and extragranular

ingredients. In another example described herein is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, wherein the pharmaceutical composition is prepared using a wet granulation method. In another example described herein is a pharmaceutical composition comprising at least 50% w/w of ibrutinib, further comprising at least one pharmaceutically acceptable excipient.

[0010] In another example described herein is a high-load solid tablet formulation comprising a pharmaceutical composition comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and one or more pharmaceutically acceptable excipients. In another example described herein is a high-load solid tablet formulation comprising a pharmaceutical composition comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and one or more pharmaceutically acceptable excipients wherein the one or more excipients are present in an amount from about 10% w/w to about 50% w/w.

[0011] In another example described herein is a high-load solid tablet formulation comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and one or more pharmaceutically acceptable excipients wherein the one or more excipients are selected from the group consisting of diluents, binders, disintegrating agents, lubricants, glidants, and surfactants. In some examples, at least one excipient is a diluent. In some examples, the diluent is selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc. In some examples, the diluent is cellulose. In some examples, the diluent is lactose; and lactose is present in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, or about 8% w/w to about 15% w/w. In some examples, the diluent is lactose; and lactose is present in an amount of about 8.5% w/w or about 14% w/w. In some examples, the diluent is microcrystalline cellulose. In some examples, the diluent is microcrystalline cellulose and the microcrystalline cellulose is present in an amount from about 1% w/w to about 20% w/w, about 1% w/w to about 10% w/w, about 1% w/w to about 5% w/w, 1% w/w to about 2% w/w, about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, or about 8% w/w to about 15% w/w. In some examples, the diluent is microcrystalline cellulose and the microcrystalline cellulose is present in an amount from about 1% w/w to about 6% w/w or about 8.5% w/w or about 14% w/w. In some examples, the diluent comprises lactose and microcrystalline cellulose. In

some examples, the lactose is present in an amount of about 10% w/w to about 15% w/w and microcrystalline cellulose is present in an amount from about 1% w/w to about 6% w/w. In some examples, the lactose is present in an amount of about 14% w/w and microcrystalline cellulose is present in an amount from about 2% w/w to about 5% w/w. In some examples, at least one excipient is a disintegrating agent. In some examples, 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, and a gum. In some examples, the disintegrating agent is croscarmellose sodium; and croscarmellose sodium is present in an amount from about 0 to about 20% w/w, about 1% w/w to about 10% w/w, about 5% w/w to about 10% w/w, about 6% w/w to about 8% w/w, about 4% w/w to about 6% w/w, or about 2% w/w to about 4% w/w. In some examples, at least one excipient is a binder. In some examples, the binder is hydroxypropyl cellulose; and hydroxypropyl cellulose is present in an amount from about 0 to about 10% w/w, about 0 to about 5% w/w, about 0 to about 2% w/w, about 0.1% w/w to about 1.1% w/w, or about 0.1% w/w to about 1% w/w. In some examples, the binder is polyvinylpyrrolidone. In some examples, the polyvinylpyrrolidone is present in an amount from about 0 to about 10% w/w, about 1 to about 5% w/w, or about 2% w/w. In some examples, the formulation comprises lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose. In some examples, at least one excipient is a surfactant. In some examples, the surfactant is sodium lauryl sulfate. In some examples, the surfactant is sodium lauryl sulfate in an amount from about 0 to about 10% w/w, about 0.5 to about 5% w/w, about 1 to about 4% w/w, about 4% w/w to about 8% w/w, or about 5% w/w to about 6% w/w. In some examples, at least one excipient is a glidant. In some examples, the glidant is silica (colloidal silicon dioxide). In some examples, the glidant is silica (colloidal silicon dioxide) and the silica (colloidal silicon dioxide) is present in an amount from about 0 to about 5% w/w, 0.1% w/w to about 1.5% w/w, about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w. In some examples, at least one excipient is a lubricant. In some examples, the lubricant is magnesium stearate. In some examples, the lubricant is magnesium stearate and the magnesium stearate is present in an amount from about 0.01% w/w to about 5% w/w, 0.01% w/w to about 2% w/w, 0.1% w/w to about 0.7% w/w, or about 0.5% w/w to about 0.6% w/w. In some examples, the excipients comprise, consist essentially of, or consist, lactose, microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate,

colloidal silicon dioxide and magnesium stearate. In another example, the excipients comprise, consist essentially of, or consist, lactose, polyvinylpyrrolidone, sodium lauryl sulfate, crospovidone, colloidal silicon dioxide, and magnesium stearate.

[0012] In another example described herein is a high-load solid tablet formulation comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and intragranular and extragranular excipients; wherein the intragranular excipients comprise, consist essentially of, or consist lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose; and the extragranular excipients comprise croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. In another example described herein is a high-load solid tablet formulation comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, wherein the intragranular excipients comprise

lactose in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 15% w/w, or about 8% w/w to about 14% w/w;

microcrystalline cellulose in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, or about 8% w/w to about 15% w/w;

croscarmellose sodium in an amount from about 0 to about 10% w/w, about 2% w/w to about 5% w/w, or about 2% w/w to about 4% w/w; and

hydroxypropyl cellulose in an amount from about 0% w/w to about 2% w/w, about 0.1% w/w to about 1.1% w/w, or about 0.1% w/w to about 1% w/w; and

the extragranular excipients comprise

croscarmellose sodium in an amount from about 0% w/w to about 5% w/w, about 2% w/w to about 5% w/w, or about 2% w/w to about 5% w/w;

sodium lauryl sulfate in an amount from about 0% w/w to about 10% w/w, about 4% w/w to about 8% w/w, or about 5% w/w to about 6% w/w;

colloidal silicon dioxide in an amount from about 0.1% w/w to about 1.5% w/w, about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w; and

magnesium stearate in an amount from about 0.1% w/w to about 1.5% w/w, about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w.

[0013] In another example described herein is a high-load solid tablet formulation comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, and intragranular and extragranular excipients; wherein the

intragranular excipients comprise lactose, microcrystalline cellulose, sodium lauryl sulfate, polyvinylpyrrolidone and croscarmellose sodium; and the extragranular excipients comprise croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. In another example described herein is a high-load solid tablet formulation comprising at least 50% w/w of ibrutinib, about 50% w/w to about 90% w/w of ibrutinib, about 50% w/w to about 80% w/w of ibrutinib, about 60% w/w to about 80% w/w of ibrutinib, or about 60% w/w to about 75% w/w of ibrutinib, wherein the intragranular excipients comprise

lactose in an amount from about 10% w/w to about 20% w/w, or about 12% w/w to about 15% w/w;

microcrystalline cellulose in an amount from about 1% w/w to about 10% w/w, about 2% w/w to about 5% w/w;

polyvinylpyrrolidone in an amount from about 0% w/w to about 5% w/w, about 1% w/w to about 3% w/w;

croscarmellose sodium in an amount from about 1% w/w to about 10% w/w, or about 3% w/w to about 7% w/w; and

sodium lauryl sulfate in an amount from about 0 to about 2% w/w, about 0.5% w/w to about 1.5% w/w; and

the extragranular excipients comprise

croscarmellose sodium in an amount from about 0 to about 5% w/w, about 1% w/w to about 3% w/w;

sodium lauryl sulfate in an amount from about 0 to about 10% w/w or about 0% w/w to about 4% w/w;

colloidal silicon dioxide in an amount from about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w; and

magnesium stearate in an amount from about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w.

[0014] In another example described herein is a high-load solid tablet formulation comprising

a) about 69% w/w to about 71% w/w of ibrutinib,

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

c) about 2% w/w to about 5% w/w of microcrystalline cellulose,

d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,

e) about 6% w/w to about 8% w/w of croscarmellose sodium,

f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,

g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

[0015] In another example described herein is a high-load solid tablet formulation comprising

a) about 70% w/w of ibrutinib,
b) about 14% w/w of lactose monohydrate,
c) about 5% w/w of microcrystalline cellulose,
d) about 2% w/w of polyvinylpyrrolidone,
e) about 7% w/w of croscarmellose sodium,
f) about 1% w/w of sodium lauryl sulfate,
g) about 0.5% w/w of colloidal silicon dioxide, and
h) about 0.5% w/w of magnesium stearate.

[0016] In another example described herein is a high-load solid tablet formulation comprising

a) about 70% w/w of ibrutinib,
b) about 14% w/w of lactose monohydrate,
c) about 2% w/w of microcrystalline cellulose,
d) about 2% w/w of polyvinylpyrrolidone,
e) about 7% w/w of croscarmellose sodium,
f) about 4% w/w of sodium lauryl sulfate,
g) about 0.5% w/w of colloidal silicon dioxide, and
h) about 0.5% w/w of magnesium stearate.

[0017] In another example described herein is a high-load solid tablet formulation comprising

a) about 70% w/w of ibrutinib,
b) about 16% w/w of lactose,
c) about 2% w/w of polyvinylpyrrolidone,
d) about 1% w/w of sodium lauryl sulfate,
e) about 10% w/w of crospovidone,
f) about 0.5% w/w of colloidal silicon dioxide, and
g) about 0.5% w/w of magnesium stearate.

[0018] In another example described herein is a high-load solid tablet formulation comprising

a) about 59% w/w to about 61% w/w of ibrutinib,
b) about 13% w/w to about 15% w/w of lactose,
c) about 13% w/w to about 15% w/w of microcrystalline cellulose,
d) about 4% w/w to about 6% w/w of croscarmellose sodium,
e) about 5% w/w to about 7% w/w of sodium lauryl sulfate,
f) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and
g) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

[0019] In some examples, the total weight of a tablet is about 934 mg.

[0020] In another example described herein is a high-load solid tablet formulation comprising

a) about 59% w/w to about 61% w/w of ibrutinib,

b) about 13% w/w to about 14% w/w of lactose,

c) about 13% w/w to about 14% w/w of microcrystalline cellulose,

d) about 2% w/w to about 3% w/w of croscarmellose sodium (intragranular),

e) about 0.8% w/w to about 1.2% w/w of hydroxypropyl cellulose,

f) about 2% w/w to about 3% w/w of croscarmellose sodium (extragranular),

g) about 5.5 to about 6.5% w/w of sodium lauryl sulfate,

h) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

i) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

[0021] In some examples, the total weight of a tablet is about 934 mg.

In another example described herein is a high-load solid tablet formulation comprising

a) about 69% w/w to about 71% w/w of ibrutinib,

b) about 8% w/w to about 9% w/w of lactose,

c) about 8 to about 9% w/w of microcrystalline cellulose,

d) about 2.5 to about 3.5% w/w of croscarmellose sodium (intragranular),

e) about 2.5 to about 3.5% w/w of croscarmellose sodium (extragranular),

g) about 5.5 to about 6.5% w/w of sodium lauryl sulfate,

h) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and

i) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

[0022] Lactose used herein may be anhydrous lactose and/or hydrous lactose, such as lactose monohydrate. In some examples, the lactose is anhydrous lactose. In some particular examples, the lacose is hydrous lactose. In more particular examples, the lacose is lactose monohydrate.

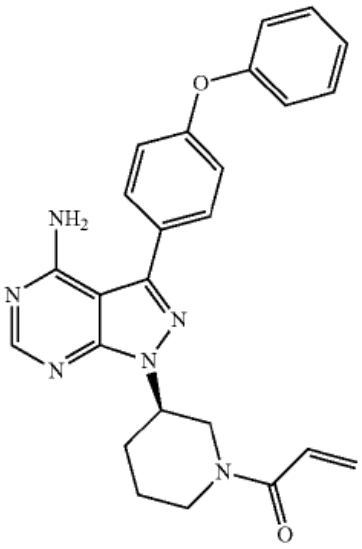
[0023] In some examples, the total weight of a tablet is about 800 mg.

[0024] In some examples of the high-load solid tablet formulations described herein, the ibrutinib is in an amount of about 35 mg to about 840 mg per tablet. In some examples of the high-load solid tablet formulations described herein, the ibrutinib is in an amount of about 140 mg to about 840 mg per tablet. In some examples of the high-load solid tablet formulations described herein, the ibrutinib is in an amount of about 140 mg, about 280 mg, about 420 mg, about 560 mg, or about 840 mg per tablet, or any range between any two of the values, end points inclusive. In some examples of the high-load solid tablet formulations described herein, the ibrutinib is in an amount of about 560 mg. In some examples of the high-load solid tablet formulations described herein, the ibrutinib is in micronized form. In some examples of the high-load solid tablet formulations described herein, the formulation

is used for once a day dosing. In some examples of the high-load solid tablet formulations described herein, the formulation is in an oral dosage form containing a therapeutically effective amount of ibrutinib.

[0024a] In one aspect, described herein is a solid tablet formulation comprising ibrutinib and one or more pharmaceutically acceptable excipients,

wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

wherein the ibrutinib is in micronized form; and

wherein ibrutinib is in an amount of about 140 mg, about 280 mg, about 420 mg, or about 560 mg in the tablet.

[0024b] In another aspect, described herein is a solid tablet formulation comprising

a. ibrutinib, and

b. one or more pharmaceutically acceptable excipients,

wherein the ibrutinib is present in an amount of at least about 50% w/w, and

wherein oral administration of one or more tablet(s) of the solid tablet formulation in an amount sufficient to deliver 560 mg of ibrutinib to a population of healthy human adults in a fasted state results in a mean $AUC_{0-\infty}$ of about 465 ng*h/ml+/−248 ng*h/ml.

[0024c] In another aspect, described herein is a solid tablet formulation comprising

a. 560 mg of ibrutinib, and

b. one or more pharmaceutically acceptable excipients,

wherein the ibrutinib is present in an amount of at least about 50% w/w, and

wherein oral administration of the solid tablet formulation to a population of healthy human adults in a fasted state results in a mean $AUC_{0-\infty}$ of about 465 ng*h/ml+/−248 ng*h/ml.

[0024d] In another aspect, described herein is a solid tablet formulation comprising

a. 560 mg of micronized ibrutinib having a particle size of about or less than 10 micron,

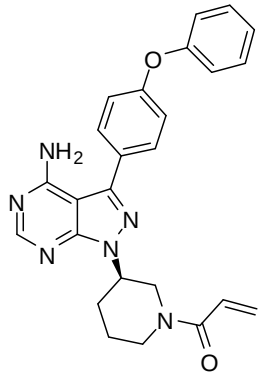
b. a surfactant, and

c. one or more additional pharmaceutically acceptable excipients,

wherein the ibrutinib is present in an amount of at least about 50% w/w, and

wherein oral administration of the solid tablet formulation to a population of healthy human adults in a fasted state results in a mean $AUC_{0-\infty}$ of about 465 ng*h/ml+/−248 ng*h/ml.

[0024e] In another aspect, described herein is a solid tablet formulation comprising ibrutinib and pharmaceutically acceptable excipients, wherein the ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the solid tablet formulation comprises about 60% w/w to about 75 % w/w of the ibrutinib, and the excipients comprise:

one or more diluents selected from group consisting of: lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc;

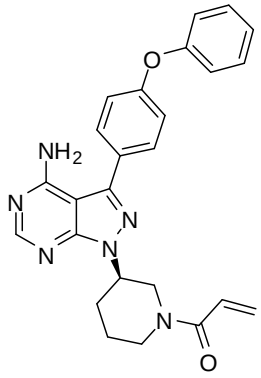
one or more disintegrating agents selected from the group consisting of: natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, crosslinked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch, cross-linked polymer, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum;

one or more binders selected from the group consisting of: hydroxypropyl cellulose, and polyvinylpyrrolidone;

colloidal silicon dioxide; and

magnesium stearate.

[0024f] In another aspect, described herein is a solid tablet formulation comprising ibrutinib and pharmaceutically acceptable excipients, wherein the ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the solid tablet formulation comprises about 60% w/w to about 75 % w/w of ibrutinib, and the excipients comprise:

microcrystalline cellulose in an amount from about 1% w/w to about 20% w/w;

croscarmellose sodium in an amount from about 1% w/w to about 10% w/w;

crospovidone in an amount from about 5% w/w to about 15% w/w;

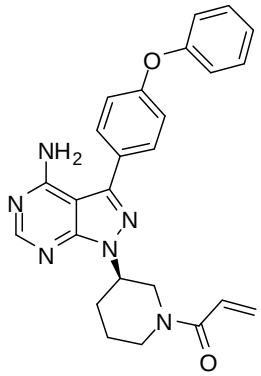
polyvinylpyrrolidone in an amount from about 1% w/w to about 5% w/w;

sodium lauryl sulfate in an amount from about 0% w/w to about 10% w/w;

colloidal silicon dioxide in an amount from about 0.1% w/w to about 1.5% w/w; and

magnesium stearate in an amount from about 0.01% w/w to about 5% w/w.

[0024g] In another aspect, described herein is a solid tablet formulation comprising ibrutinib and pharmaceutically acceptable excipients, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

about 60% w/w to about 75 % w/w of the ibrutinib,

wherein the excipients comprise intragranular and extragranular excipients; wherein the intragranular excipients comprise microcrystalline cellulose and polyvinylpyrrolidone; and

wherein extragranular excipients comprise croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

[0025] In another example described herein 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.

[0026] In another example described herein is a method of treating an autoimmune 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 some examples, the autoimmune disease is rheumatoid arthritis or lupus.

[0027] In another example described herein is a method of treating a heteroimmune 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.

[0028] In another example described herein is a method of treating cancer 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 some examples, the cancer is a B-cell proliferative disorder. In some examples, the cancer is a B-cell proliferative disorder and the B-cell proliferative disorder is diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia. In some examples, the cancer is a B cell malignancy.

In some examples, the cancer is a B cell malignancy and the 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 examples, the cancer is a lymphoma, leukemia or a solid tumor. In some examples, 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.

[0029] In another example described herein is a method of treating mastocytosis 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.

[0030] In another example described herein is a method of treating osteoporosis or bone resorption disorders 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.

[0031] In another example described herein is a method of treating an inflammatory disease or condition 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.

[0032] In another example described herein is a method of treating lupus 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.

[0033] In some examples, the formulations and methods described herein can be used to treat carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina, cervix, testis, genitourinary tract, esophagus, larynx, skin, bone or thyroid, sarcoma, glioblastomas, neuroblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, adenoma, adenocarcinoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small-cell lung carcinoma, lymphomas, Hodgkins and Non-Hodgkins, a mammary carcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, or Smoldering of indolent multiple myeloma.

[0034] In some examples, the formulations and methods described herein can be used to treat a central nervous system (CNS) malignancy. In some examples, the CNS malignancy is a primary CNS lymphoma. In some examples the primary CNS lymphoma is a glioma. In some examples the glioma is astrocytomas, ependymomas, oligodendrogliomas. In some examples the CNS malignancy is astrocytic tumors such as juvenile pilocytic, subependymal, well differentiated or moderately differentiated anaplastic astrocytoma; anaplastic astrocytoma; glioblastoma multiforme; ependymal tumors such as myxopapillary and well-differentiated ependymoma, anaplastic ependymoma, ependymoblastoma; oligodendroglial tumors including well-differentiated oligodendroglioma and anaplastic oligodendroglioma; mixed tumors such as mixed astrocytoma-ependymoma, mixed astrocytoma-oligodendroglioma, mixed astrocytomaependymoma-oligodendroglioma; or medulloblastoma.

[0035] In some examples, the formulations and methods described herein can be used to treat hematological malignancies such as, but not limited to, a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some examples, the hematological malignancy is a treatment naïve

hematological malignancy. In some examples the hematological malignancy is a relapsed or refractory hematological malignancy.

[0036] In some examples, the hematologic malignancy is a T-cell malignancy. In some examples, the T-cell malignancy is peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, or treatment-related T-cell lymphomas. In some examples, the T-cell malignancy is a relapsed or refractory T-cell malignancy. In some examples, the T-cell malignancy is a treatment naïve T-cell malignancy.

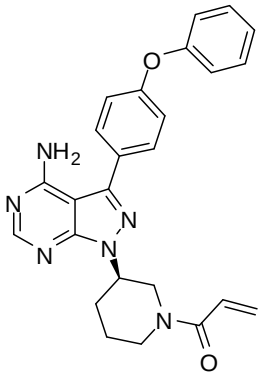
[0037] In some examples, the hematologic malignancy is a B-cell proliferative disorder. In some examples, the cancer is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, or prolymphocytic leukemia (PLL). In some examples, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis. In some examples, DLBCL is further divided into subtypes: activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), germinal center diffuse large B-cell lymphoma (GCB DLBCL), and Double-Hit (DH) DLBCL. In some examples, ABC-DLBCL is characterized by a CD79B mutation. In some examples, ABC-DLBCL is characterized by a CD79A mutation. In some examples, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some examples, the cancer is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia. In some examples, the B-cell proliferative disorder is a relapsed and refractory B-cell proliferative disorder. In some examples, the B-cell proliferative disorder is a treatment naïve B-cell proliferative disorder.

[0038] In some examples, the formulations and methods described herein can be used to treat fibrosis. In some examples, the fibrosis is not associated with graft versus host disease (GVHD). In some examples, the fibrosis is not associated with sclerodermatous GVHD, lung chronic GVHD, or liver chronic GVHD. In some examples, the fibrosis is of the liver,

lung, pancreas, kidney, bone marrow, heart, skin, intestine, or joints. In some examples, the fibrosis is of the liver. In some examples, the fibrosis is of the lung. In some examples, the fibrosis is of the pancreas. In some examples, the patient has cirrhosis, chronic pancreatitis, or cystic fibrosis.

[0039] Described herein is a process for preparing a pharmaceutical composition or tablet formulation comprising ibrutinib as described herein, wherein the process comprises a wet granulation method.

[0040] Described herein is a high-load solid tablet formulation comprising ibrutinib, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and the tablet comprises about 560 mg of ibrutinib.

[0041] In another example described herein is a high-load solid tablet formulation, wherein ibrutinib is in micronized form. In another example, ibrutinib is in spray-dried form. In another example, ibrutinib is not in spray-dried form. In another example, the particle size is about or less than 30 micron. In one example, ibrutinib is in micronized form and the particle size is about 1-30 micron. In another example, the particle size is about or less than 10 micron. In another example, the particle size is <1 micron. In another example is a high-load solid tablet formulation, wherein the tablet is used for once a day oral dosing.

[0042] Provided herein are methods for treating a patient by administering Compound 1. In some examples, provided herein is a method of inhibiting the activity of tyrsoine 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.

[0043] 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.

[0044] In some examples, a pharmaceutical composition comprising crystalline Compound 1 is administered to a human. In some examples, a pharmaceutical composition comprising amorphous Compound 1 is administered to a human.

[0045] In some examples, a pharmaceutical composition comprising crystalline Compound 1 is orally administered. In some examples, a pharmaceutical composition comprising amorphous Compound 1 is orally administered.

[0046] In some examples, a pharmaceutical composition comprising crystalline Compound 1 is used for the formulation of a medicament for the inhibition of tyrosine kinase activity. In some other examples, a pharmaceutical composition comprising crystalline Compound 1 is used for the formulation of a medicament for the inhibition of Bruton's tyrosine kinase (Btk) activity. In some examples, a pharmaceutical composition comprising amorphous Compound 1 is used for the formulation of a medicament for the inhibition of tyrosine kinase activity. In some other examples, a pharmaceutical composition comprising amorphous Compound 1 is used for the formulation of a medicament for the inhibition of Bruton's tyrosine kinase (Btk) activity.

[0047] In any of the examples disclosed herein (including compositions, 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 any of the examples disclosed herein (including compositions, 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.

[0048] In any of the examples disclosed herein (including compositions, methods, uses, formulations, combination therapy, etc.), amorphous Compound 1 is used. In any of the examples disclosed herein (including compositions, methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 is used.

[0049] In any of the examples disclosed herein (including compositions, 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 examples, the active metabolite is in a crystalline form. In some examples, the active metabolite is in an amorphous phase. In further examples the metabolite is isolated.

In any of the examples disclosed herein (including compositions, methods, uses, formulations, combination therapy, etc.), Compound 1, or a pharmaceutically acceptable salt thereof, is replaced with a prodrug of Compound 1, or a deuterated analog of Compound 1, or a pharmaceutically acceptable salt thereof.

[0050] 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 examples, 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

[0051] 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

[0052] FIG. 1 shows mean plasma concentration-time profiles of ibrutinib following single oral dose administration of a capsule formulation versus three different wet tablet formulations to fasted beagle dogs (Dose = 140 mg).

[0053] FIG. 2 shows mean plasma concentration-time profiles of ibrutinib following single oral dose administration of a capsule formulation versus two different dry tablet formulations to fasted beagle dogs (Dose = 140 mg).

[0054] FIG. 3 is a photo of examples: (A) a capsule comprising 140 mg ibrutinib (Formulation A), and tablets of the invention (B-E) comprising 560 mg, 420 mg, 280 mg, and 140 mg of ibrutinib, respectively.

DETAILED DESCRIPTION OF THE INVENTION

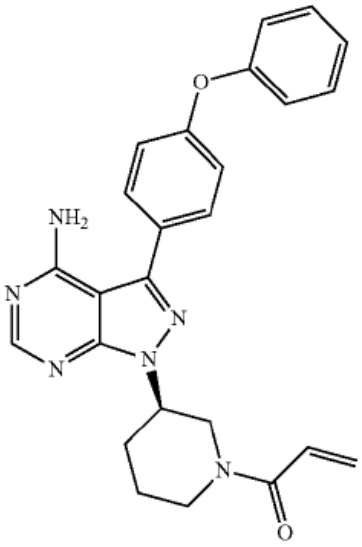
[0055] The diverse roles played by Btk signaling in various hematopoietic cell functions, e.g., B-cell receptor activation, suggests that small molecule Btk inhibitors, such as Compound 1, are useful for reducing the risk of or treating a variety of diseases affected by or affecting many cell types of 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

CLAIMS

WHAT IS CLAIMED IS:

1. A solid tablet formulation comprising ibrutinib and one or more pharmaceutically acceptable excipients,

wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

wherein the ibrutinib is in micronized form; and

wherein ibrutinib is in an amount of about 140 mg, about 280 mg, about 420 mg, or about 560 mg in the tablet.

2. The solid tablet formulation of claim 1, wherein the particle size of micronized ibrutinib is about or less than 30 microns.

3. The solid tablet formulation of claim 1, wherein the particle size of micronized ibrutinib is about or less than 10 microns.

4. The solid tablet formulation of claim 1, wherein the particle size of micronized ibrutinib is less than about 1 micron.

5. The solid tablet formulation of claim 1 further comprising one or more diluents.

6. The solid tablet formulation of claim 5, wherein the one or more diluents are selected from the group consisting of lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc.

7. The solid tablet formulation of claim 5, wherein the one or more diluents are lactose, cellulose, microcrystalline cellulose, or a combination thereof.

8. The solid tablet formulation of claim 5 further comprising one or more lubricants.

9. The solid tablet formulation of claim 8, wherein the one or more lubricants are a stearate, a polyethylene glycol (PEG), or a wax.

10. The solid tablet formulation of claim 8 further comprising one or more disintegrating agents.

11. The solid tablet formulation of claim 10, wherein the one or more disintegrating agents are 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, cross-linked polymer, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum.

12. The solid tablet formulation of claim 10, wherein the one or more disintegrating agents are 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, sodium starch glycolate, crospovidone, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum.

13. The solid tablet formulation of claim 8 further comprising one or more binders.

14. The solid tablet formulation of claim 13, wherein the one or more binders are polyvinylpyrrolidone or hydroxypropyl cellulose.

15. The solid tablet formulation of claim 1 comprising:
a. at least 50% w/w of ibrutinib;
b. one or more diluents; and
c. one or more lubricants.

16. The solid tablet formulation of claim 1 comprising:
a. about 50% w/w to about 90% w/w of ibrutinib;
b. about 5% w/w to about 20% w/w of one or more diluents; and
c. about 0.1% w/w to about 1.5% w/w of one or more lubricants.

17. The solid tablet formulation of claim 1, wherein the excipients comprise intragranular and extragranular excipients; and the intragranular excipients comprise one or more diluents; and the extragranular excipients comprise one or more lubricants.

18. The solid tablet formulation of claim 1, wherein the excipients comprise intragranular and extragranular excipients; and the intragranular excipients comprise lactose and microcrystalline cellulose; and the extragranular excipients comprise magnesium stearate.

19. The solid tablet formulation of claim 1, wherein the excipients comprise lactose in an amount from about 5% w/w to about 20% w/w, about 10% w/w to about 20% w/w, about 8% w/w to about 15% w/w, about 8.5% w/w to about 14% w/w, or about 12% w/w to about 15% w/w.

20. The solid tablet formulation of claim 1, wherein the excipients comprise microcrystalline cellulose in an amount from about 5% w/w to about 20% w/w, about 8% w/w to about 20% w/w, about 8% w/w to about 15% w/w, about 1% w/w to about 10% w/w, or about 2% w/w to about 5% w/w.

21. The solid tablet formulation of claim 1, wherein the excipients comprise magnesium stearate in an amount from about 0.1% w/w to about 1.5% w/w, about 0.4% w/w to about 0.8% w/w, or about 0.5% w/w to about 0.6% w/w.

22. The solid tablet formulation of claim 1, wherein the excipients comprise intragranular and extragranular excipients; and the intragranular excipients comprise lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose; and the extragranular excipients comprise croscarmellose sodium and magnesium stearate.

23. The solid tablet formulation of claim 1, wherein the excipients comprise croscarmellose sodium in an amount from about 0% w/w to about 10% w/w, about 0% w/w to about 5% w/w,

about 1% w/w to about 10% w/w, about 2% w/w to about 5% w/w, about 2% w/w to about 4% w/w, about 3% w/w to about 7% w/w, or about 1% w/w to about 3% w/w.

24. The solid tablet formulation of claim 1, wherein the excipients comprise hydroxypropyl cellulose in an amount from about 0% w/w to about 2% w/w, about 0.1% w/w to about 1.1% w/w, or about 0.1% w/w to about 1% w/w.

25. The solid tablet formulation of claim 1, wherein the excipients comprise intragranular and extragranular excipients; and the intragranular excipients comprise lactose, polyvinylpyrrolidone, and croscarmellose sodium; and the extragranular excipients comprise croscarmellose sodium, microcrystalline cellulose, and magnesium stearate.

26. The solid tablet formulation of claim 1, wherein the excipients comprise polyvinylpyrrolidone in an amount from about 0% w/w to about 5% w/w, or about 1% w/w to about 3% w/w.

27. The solid tablet formulation of claim 1, wherein the formulation is used for one tablet once a day dosing.

28. The solid tablet formulation of claim 1, wherein the formulation comprises about 60% w/w to about 80% w/w of ibrutinib.

29. A solid tablet formulation comprising
a. ibrutinib, and
b. one or more pharmaceutically acceptable excipients,
wherein the ibrutinib is present in an amount of at least about 50% w/w, and
wherein oral administration of one or more tablet(s) of the solid tablet formulation in an amount sufficient to deliver 560 mg of ibrutinib to a population of healthy human adults in a fasted state results in a mean $AUC_{0-\infty}$ of about 465 ng*h/ml+/−248 ng*h/ml.

30. The solid tablet formulation of claim 29, wherein the ibrutinib is present in an amount of at least about 60% w/w.

31. The solid tablet formulation of claim 29, comprising 420 mg of ibrutinib.

32. The solid tablet formulation of claim 29, wherein the ibrutinib is present in micronized form.

33. The solid tablet formulation of claim 32, wherein the particle size of micronized ibrutinib is about or less than 30 micron.

34. The solid tablet of any one of claims 29–33, further comprising a surfactant.

35. A solid tablet formulation comprising
a. 560 mg of ibrutinib, and
b. one or more pharmaceutically acceptable excipients,
wherein the ibrutinib is present in an amount of at least about 50% w/w, and
wherein oral administration of the solid tablet formulation to a population of healthy human adults in a fasted state results in a mean $AUC_{0-\infty}$ of about 465 ng*h/ml+/−248 ng*h/ml.

36. The solid tablet formulation of claim 35, wherein the ibrutinib is present in an amount of at least about 60% w/w.

37. The solid tablet formulation of claim 35, wherein the ibrutinib is present in micronized form.

38. The solid tablet formulation of claim 37, wherein the particle size of micronized ibrutinib is about or less than 30 micron.

39. The solid tablet formulation of claim 37, wherein the particle size of micronized ibrutinib is about or less than 10 micron.

40. The solid tablet formulation of any one of claims 35–39, further comprising a surfactant.

41. A solid tablet formulation comprising
a. 560 mg of micronized ibrutinib having a particle size of about or less than 10 micron,
b. a surfactant, and
c. one or more additional pharmaceutically acceptable excipients,
wherein the ibrutinib is present in an amount of at least about 50% w/w, and

wherein oral administration of the solid tablet formulation to a population of healthy human adults in a fasted state results in a mean $AUC_{0-\infty}$ of about 465 ng*h/ml+/−248 ng*h/ml.

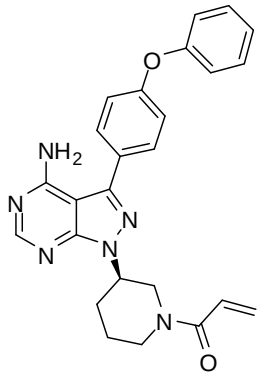
42. The solid tablet formulation of claim 29, comprising 140 mg of ibrutinib.

43. The solid tablet formulation of claim 29, comprising 280 mg of ibrutinib.

44. The solid tablet formulation of claim 29, comprising 560 mg of ibrutinib.

45. The solid tablet formulation of any one of claims 29–44, wherein the solid tablet formulation has pharmaceutically acceptable stability.

46. A solid tablet formulation comprising ibrutinib and pharmaceutically acceptable excipients, wherein the ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the solid tablet formulation comprises about 60% w/w to about 75 % w/w of the ibrutinib, and the excipients comprise:

one or more diluents selected from group consisting of: lactose, sucrose, dextrose, dextrates, maltodextrin, mannitol, xylitol, sorbitol, cyclodextrins, calcium phosphate, calcium sulfate, starches, modified starches, cellulose, microcrystalline cellulose, microcellulose, and talc;

one or more disintegrating agents selected from the group consisting of: natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, crosslinked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, cross-linked starch, cross-linked polymer, cross-linked polyvinylpyrrolidone, sodium alginate, a clay, and a gum;

one or more binders selected from the group consisting of: hydroxypropyl cellulose, and polyvinylpyrrolidone;
colloidal silicon dioxide; and
magnesium stearate.

47. The solid tablet formulation of claim 46, wherein the one or more disintegrating agents are selected from the group consisting of croscarmellose sodium, and crospovidone.

48. The solid tablet formulation of claim 46, wherein the diluent is microcrystalline cellulose.

49. The solid tablet formulation of claim 46, wherein the binder is polyvinylpyrrolidone.

50. The solid tablet formulation of claim 46, wherein the excipients comprise microcrystalline cellulose, crospovidone, polyvinylpyrrolidone, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

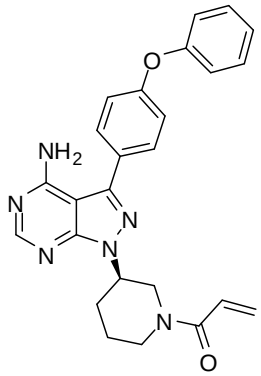
51. The solid tablet formulation of claim 46, wherein the colloidal silicon dioxide is present in an amount from about 0.1% w/w to about 1.5% w/w.

52. The solid tablet formulation of claim 46, wherein the magnesium stearate is present in an amount from about 0.01% w/w to about 5% w/w.

53. The solid tablet formulation of claim 46, wherein the magnesium stearate is present in an amount from about 0.01% w/w to about 2% w/w.

54. The solid tablet formulation of claim 46, wherein the magnesium stearate is present in an amount from about 0.1% w/w to about 0.7% w/w.

55. A solid tablet formulation comprising ibrutinib and pharmaceutically acceptable excipients, wherein the ibrutinib is a compound with the structure of Compound 1,



Compound 1;

and wherein the solid tablet formulation comprises about 60% w/w to about 75 % w/w of ibrutinib, and the excipients comprise:

microcrystalline cellulose in an amount from about 1% w/w to about 20% w/w;

croscarmellose sodium in an amount from about 1% w/w to about 10% w/w;

crospovidone in an amount from about 5% w/w to about 15% w/w;

polyvinylpyrrolidone in an amount from about 1% w/w to about 5% w/w;

sodium lauryl sulfate in an amount from about 0% w/w to about 10% w/w;

colloidal silicon dioxide in an amount from about 0.1% w/w to about 1.5% w/w; and

magnesium stearate in an amount from about 0.01% w/w to about 5% w/w.

56. The solid tablet formulation of claim 55, wherein the microcrystalline cellulose is present in an amount from about 1% w/w to about 10% w/w.

57. The solid tablet formulation of claim 55, wherein the microcrystalline cellulose is present in an amount from about 5% w/w to about 20% w/w.

58. The solid tablet formulation of claim 55, wherein the microcrystalline cellulose is present in an amount from about 8% w/w to about 20% w/w.

59. The solid tablet formulation of claim 55, wherein the microcrystalline cellulose is present in an amount from about 8% w/w to about 15% w/w.

60. The solid tablet formulation of claim 55, wherein the croscarmellose sodium is present in an amount from about 5% w/w to about 10% w/w.

61. The solid tablet formulation of claim 55, wherein the polyvinylpyrrolidone is present in an amount from about 1% w/w to about 3% w/w.

62. The solid tablet formulation of claim 55, wherein the sodium lauryl sulfate is present in an amount from about 0.5% w/w to about 5% w/w.

63. The solid tablet formulation of claim 55, wherein the colloidal silicon dioxide is present in an amount from about 0.4% w/w to about 0.8% w/w.

64. The solid tablet formulation of claim 55, wherein the magnesium stearate is present in an amount from about w/w 0.1% w/w to about 1.5% w/w.

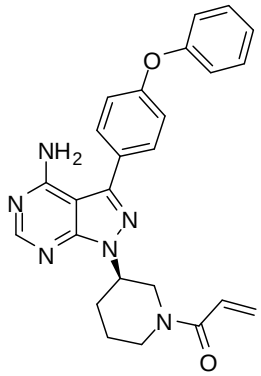
65. The solid tablet formulation of claim 55, wherein the magnesium stearate is present in an amount from about 0.01% w/w to about 2% w/w.

66. The solid tablet formulation of claim 55, wherein the magnesium stearate is present in an amount from about 0.1% w/w to about 0.7% w/w.

67. The solid tablet formulation of claim 55, wherein the microcrystalline cellulose is present in an amount from about 1% w/w to about 10% w/w;
wherein the croscarmellose sodium is present in an amount from about 5% w/w to about 10% w/w;
wherein the polyvinylpyrrolidone is present in an amount from about 1% w/w to about 3% w/w; and
wherein the magnesium stearate is present in an amount from about w/w 0.01% w/w to about 5% w/w.

68. The solid tablet formulation of claim 55, wherein ibrutinib is present in an amount of about 140 mg, about 280 mg, about 420 mg, or about 560 mg.

69. A solid tablet formulation comprising ibrutinib and pharmaceutically acceptable excipients, wherein ibrutinib is a compound with the structure of Compound 1,



Compound 1;

about 60% w/w to about 75 % w/w of the ibrutinib,

wherein the excipients comprise intragranular and extragranular excipients; wherein the intragranular excipients comprise microcrystalline cellulose and polyvinylpyrrolidone; and

wherein extragranular excipients comprise croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate.

70. The solid tablet formulation of claim 69, wherein the extragranular excipients further comprise microcrystalline cellulose.