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.

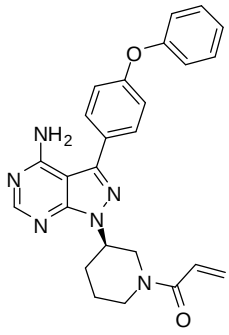
SUMMARY ~~OF THE INVENTION~~

[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, 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] ~~In one aspect~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiments~~examples, at least one excipient is a diluent. In some ~~embodiments~~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 ~~embodiments~~examples, the diluent is cellulose. In some ~~embodiments~~examples, the diluent is ~~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 ~~embodiments~~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 ~~embodiments~~examples, the diluent is microcrystalline cellulose. In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~examples, the diluent comprises lactose and microcrystalline cellulose. In

some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~examples, at least one excipient is a disintegrating agent. In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~examples, at least one excipient is a binder. In some ~~embodiments~~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 ~~embodiments~~examples, the binder is polyvinylpyrrolidone. In some ~~embodiments~~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 ~~embodiments~~examples, the formulation comprises lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose. In some ~~embodiments~~examples, at least one excipient is a surfactant. In some ~~embodiments~~examples, the surfactant is sodium lauryl sulfate. In some ~~embodiments~~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 ~~embodiments~~examples, at least one excipient is a glidant. In some ~~embodiments~~examples, the glidant is silica (colloidal silicon dioxide). In some ~~embodiments~~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 ~~embodiments~~examples, at least one excipient is a lubricant. In some ~~embodiments~~examples, the lubricant is magnesium stearate. In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiment~~example, the excipients comprise, consist essentially of, or consist, lactose, polyvinylpyrrolidone, sodium lauryl sulfate, crospovidone, colloidal silicon dioxide, and magnesium stearate.

[0012] In another ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiments~~examples, the total weight of a tablet is about 934 mg.

[0020] In another ~~embodiment~~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 ~~embodiments~~examples, the total weight of a tablet is about 934 mg.

In another ~~embodiment~~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 ~~embodiments~~examples, the lactose is anhydrous lactose. In some particular ~~embodiments~~examples, the lacose is hydrous lactose. In more particular ~~embodiments~~examples, the lacose is lactose monohydrate.

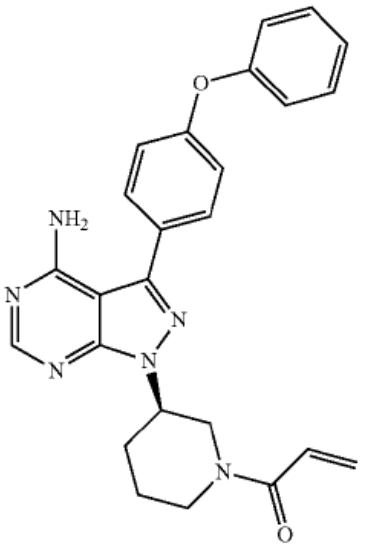
[0023] In some ~~embodiments~~examples, the total weight of a tablet is about 800 mg.

[0024] In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~examples of the high-load solid tablet formulations described herein, the ibrutinib is in an amount of about 560 mg. In some ~~embodiments~~examples of the high-load solid tablet formulations described herein, the ibrutinib is in micronized form. In some ~~embodiments~~examples of the high-load solid tablet formulations described herein, the formulation

is used for once a day dosing. In some ~~embodiments~~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,

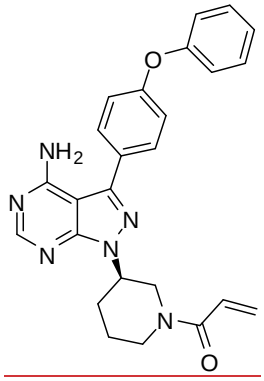
b. a surfactant, and

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;

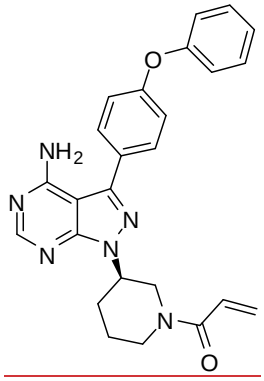
one or more disintegrating agents selected from the group consisting of: natural starch, a pregelatinized starch, a sodium starch, methylcrystalline cellulose, methylcellulose, croscarmellose, croscarmellose sodium, crosslinked sodium carboxymethylcellulose, cross-linked carboxymethylcellulose, cross-linked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

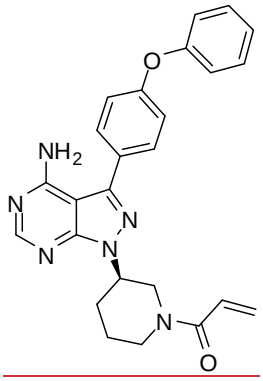
polyvinylpyrrolidone in an amount from about 1% w/w to about 5% w/w;

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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiments~~examples, the autoimmune disease is rheumatoid arthritis or lupus.

[0027] In another ~~embodiment~~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 ~~embodiment~~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 ~~embodiments~~examples, the cancer is a B-cell proliferative disorder. In some ~~embodiments~~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 ~~embodiments~~examples, the cancer is a B cell malignancy.

In some ~~embodiments~~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 ~~embodiments~~examples, the cancer is a lymphoma, leukemia or a solid tumor. In some ~~embodiments~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiments~~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 ~~embodiments~~examples, the formulations and methods described herein can be used to treat a central nervous system (CNS) malignancy. In some ~~embodiments~~examples, the CNS malignancy is a primary CNS lymphoma. In some ~~embodiments~~examples the primary CNS lymphoma is a glioma. In some ~~embodiments~~examples the glioma is astrocytomas, ependymomas, oligodendrogliomas. In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~examples, the hematological malignancy is a treatment naïve

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

[0036] In some ~~embodiments~~examples, the hematologic malignancy is a T-cell malignancy. In some ~~embodiments~~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 ~~embodiments~~examples, the T-cell malignancy is a relapsed or refractory T-cell malignancy. In some ~~embodiments~~examples, the T-cell malignancy is a treatment naïve T-cell malignancy.

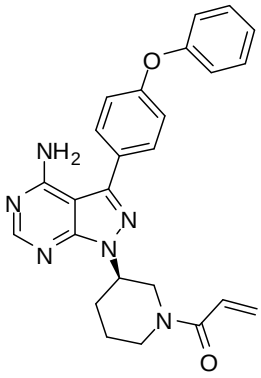
[0037] In some ~~embodiments~~examples, the hematologic malignancy is a B-cell proliferative disorder. In some ~~embodiments~~examples, the cancer is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, or prolymphocytic leukemia (PLL). In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~examples, ABC-DLBCL is characterized by a CD79B mutation. In some ~~embodiments~~examples, ABC-DLBCL is characterized by a CD79A mutation. In some ~~embodiments~~examples, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some ~~embodiments~~examples, the cancer is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia. In some ~~embodiments~~examples, the B-cell proliferative disorder is a relapsed and refractory B-cell proliferative disorder. In some ~~embodiments~~examples, the B-cell proliferative disorder is a treatment naïve B-cell proliferative disorder.

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

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

[0039] ~~In another aspect~~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] ~~In another aspect~~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 ~~embodiment~~example described herein is a high-load solid tablet formulation, wherein ibrutinib is in micronized form. In another ~~embodiment~~example, ibrutinib is in spray-dried form. In another ~~embodiment~~example, ibrutinib is not in spray-dried form. In another ~~embodiment~~example, the particle size is about or less than 30 micron. In one ~~embodiment~~example, ibrutinib is in micronized form and the particle size is about 1-30 micron. In another ~~embodiment~~example, the particle size is about or less than 10 micron. In another ~~embodiment~~example, the particle size is <1 micron. In another ~~embodiment~~example is a high-load solid tablet formulation, wherein the tablet is used for once a day oral dosing.

[0042] ~~In another aspect, provided~~Provided herein are methods for treating a patient by administering Compound 1. In some ~~embodiments~~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] ~~In another aspect, provided~~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 ~~embodiments~~examples, a pharmaceutical composition comprising crystalline Compound 1 is administered to a human. In some ~~embodiments~~examples, a pharmaceutical composition comprising amorphous Compound 1 is administered to a human.

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

[0046] In some ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~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 ~~embodiments~~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 ~~some embodiments, in~~ any of the ~~embodiments~~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 ~~some embodiments, in~~ any of the ~~embodiments~~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 ~~embodiments~~examples disclosed herein (including compositions, methods, uses, formulations, combination therapy, etc.), amorphous Compound 1 is used. In any of the ~~embodiments~~examples disclosed herein (including compositions, methods, uses, formulations, combination therapy, etc.), crystalline Compound 1 is used.

[0049] In ~~some embodiments, in~~ any of the ~~embodiments~~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 ~~embodiments~~examples, the active metabolite is in a crystalline form. In some ~~embodiments~~examples, the active metabolite is in an amorphous phase. In further ~~embodiments~~examples the metabolite is isolated.

In ~~some embodiments, in~~ any of the ~~embodiments~~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 ~~embodiments~~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.

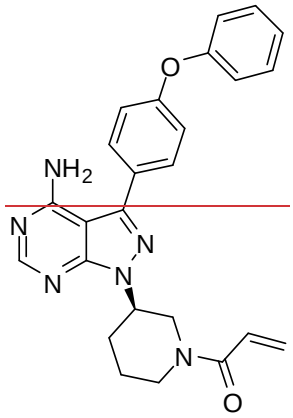
DETAILED DESCRIPTION OF THE INVENTION

[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 high-load 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;

and wherein the high-load solid tablet formulation comprises at least 50% w/w of ibrutinib.

2. The high-load solid tablet formulation of claim 1, wherein the high-load solid tablet formulation comprises about 50% w/w to about 90% w/w of ibrutinib.

3. The high-load solid tablet formulation of claim 1, wherein the high-load solid tablet formulation comprises about 50% w/w to about 80% w/w of ibrutinib.

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

5. The high-load solid tablet formulation of claim 1, wherein the high-load solid tablet formulation comprises about 60% w/w to about 75% w/w of ibrutinib.

6. The high-load solid tablet formulation of any one of claims 1-5, wherein the high-load solid tablet formulation comprises intragranular and extragranular ingredients.

7. The high-load solid tablet formulation of any one of claims 1-6, wherein the one or more excipients are selected from the group consisting of diluents, binders, disintegrating agents, lubricants, glidants, and surfactants.

8. The high-load solid tablet formulation of any one of claims 1-7, wherein at least one excipient is a diluent.

9. The high-load solid tablet formulation of claim 8, wherein 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.

10. The high-load solid tablet formulation of claim 8, wherein the diluent is cellulose.

~~11. The high-load solid tablet formulation of claim 8, wherein 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.~~

~~12. The high-load solid tablet formulation of claim 8, wherein the diluent is lactose; and lactose is present in an amount of about 8.5% w/w or about 14% w/w.~~

~~13. The high-load solid tablet formulation of claim 8, wherein the diluent is microcrystalline cellulose.~~

~~14. The high-load solid tablet formulation of claim 13, wherein the microcrystalline cellulose 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.~~

~~15. The high-load solid tablet formulation of claim 13, wherein the microcrystalline cellulose is present in an amount of about 8.5% w/w or about 14% w/w.~~

~~16. The high-load solid tablet formulation of claim 8, wherein the diluent is lactose and microcrystalline cellulose.~~

~~17. The high-load solid tablet formulation of claim 16, wherein 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.~~

~~18. The high-load solid tablet formulation of claim 16, wherein 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.~~

~~19. The high-load solid tablet formulation of any one of claims 1-18, wherein at least one excipient is a disintegrating agent.~~

~~20. The high-load solid tablet formulation of claim 19, wherein 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.~~

~~21. The high-load solid tablet formulation of claim 19, wherein 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.~~

~~22. The high-load solid tablet formulation of any one of claims 1-21, wherein at least one excipient is a binder.~~

~~23. The high-load solid tablet formulation of claim 22, wherein 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.~~

~~24. The high-load solid tablet formulation of any one of claims 1-23, wherein the formulation comprises lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose.~~

~~25. The high-load solid tablet formulation of claim 22, wherein the binder is polyvinylpyrrolidone.~~

~~26. The high-load solid tablet formulation of claim 25, wherein, 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.~~

~~27. The high-load solid tablet formulation of any one of claims 1-26, wherein at least one excipient is a surfactant.~~

~~28. The high-load solid tablet formulation of claim 27, wherein the surfactant is sodium lauryl sulfate.~~

~~29. The high-load solid tablet formulation of claim 28, wherein the sodium lauryl sulfate is present 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.~~

~~30. The high-load solid tablet formulation of any one of claims 1-29, wherein the formulation further comprises one or more glidants.~~

~~31. The high-load solid tablet formulation of claim 30, wherein the glidant is silica (colloidal silicon dioxide).~~

~~32. The high-load solid tablet formulation of claim 31, wherein 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.~~

~~33. The high-load solid tablet formulation of any one of claims 1-32, wherein at least one excipient is a lubricant.~~

~~34. The high-load solid tablet formulation of claim 33, wherein the lubricant is magnesium stearate.~~

~~35. The high-load solid tablet formulation of claim 34, wherein 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.~~

~~36. The high-load solid tablet formulation of any one of claims 1-22 and 25-35, wherein the excipients comprise lactose, microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide and magnesium stearate.~~

~~37. The high-load solid tablet formulation of any one of claims 1-5, wherein the formulation comprises intragranular and extragranular excipients; and the intragranular excipients comprise lactose, microcrystalline cellulose, croscarmellose sodium, and hydroxypropyl cellulose; and the extragranular excipients comprise croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate.~~

~~38. The high-load solid tablet formulation of any one of claims 1-5, 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 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 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 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.~~

~~39. The high-load solid tablet formulation of any one of claims 1-5, wherein the formulation comprises intragranular and extragranular excipients; and the intragranular excipients comprise lactose, sodium lauryl sulfate, polyvinylpyrrolidone and croscarmellose sodium; and the extragranular excipients comprise croscarmellose sodium, sodium lauryl sulfate, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.~~

~~40. The high-load solid tablet formulation of any one of claims 1-5, 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;~~

~~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 % w/w 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 % w/w to about 5% w/w, about 1% w/w to about 3% w/w;~~

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

~~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.~~

~~41. The high-load solid tablet formulation of claim 1, 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 monohydrate,~~

~~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.~~

~~42. The high-load solid tablet formulation of claim 1, 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.

43. The high-load solid tablet formulation of claim 1, 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.

44. The high-load solid tablet formulation of claim 1, wherein the formulation comprises:

a) about 65% w/w to about 75% w/w of ibrutinib,

b) about 14% w/w to about 18% w/w of lactose monohydrate,

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

d) about 0.5% w/w to about 1.5% w/w of sodium lauryl sulfate,

e) about 5% w/w to about 15% w/w of crospovidone,

f) about 0.3% w/w to about 0.7% w/w of colloidal silicon dioxide, and

g) about 0.3% w/w to about 0.7% w/w of magnesium stearate.

45. The high-load solid tablet formulation of claim 1, wherein the formulation comprises:

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.

46. The high-load solid tablet formulation of claim 1, wherein the formulation comprises:

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% w/w 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.

47. The high-load solid tablet formulation of claim 1, wherein the formulation comprises:

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% w/w to about 9% w/w of microcrystalline cellulose,

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

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

g) about 5.5% w/w 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.

48. The high-load solid tablet formulation of any one of claims 1-47, wherein ibrutinib is in an amount of about 420 or about 560 mg.

49. The high-load solid tablet formulation of any one of claims 1-48, wherein the high-load solid tablet formulation is used for one tablet once a day dosing.

50. The high-load solid tablet formulation of any one of claims 1-49, wherein the high-load solid tablet formulation is prepared using a process comprising a wet granulation method.

51. 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 high-load solid tablet formulation of any one of claims 1-49.

52. A process for preparing the high-load solid tablet formulation of any one of claims 1-49, wherein the process comprises a wet granulation method.

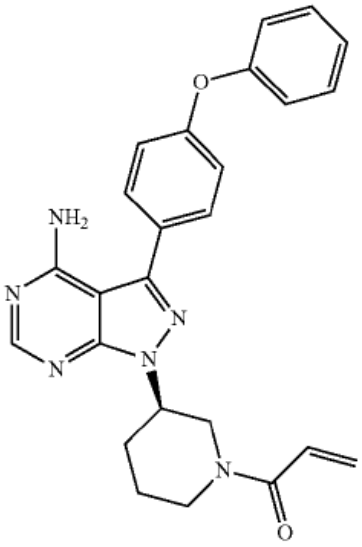
53. The process of claim 52, wherein the wet granulation method comprises granulating a mixture of ibrutinib and the intragranular excipients with a granulation liquid to form granules.

54. The process of claim 52 or 53, comprising (1) mixing ibrutinib with the intragranular excipients; (2) granulating the mixture of ibrutinib and the intragranular excipients with purified water or an aqueous binder solution to form granules; (3) drying the granules to form dried granules; (4) milling the dried granules; (5) blending the milled granules with the

~~extragranular excipients; and (6) compressing the mixture of milled granules and the extragranular excipients to form tablets of the high-load solid tablet formulation.~~

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.

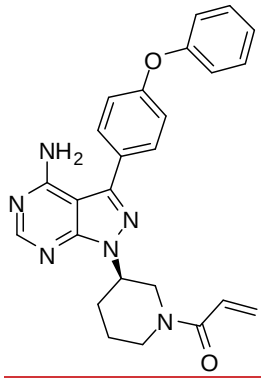
42. The solid tablet formulation of claim 29, comprising 140 mg of ibrutinib.

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.

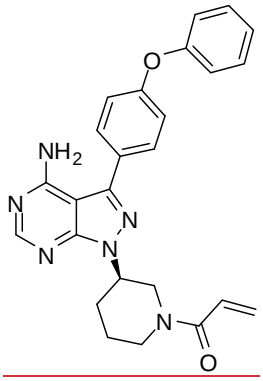
51. The solid tablet formulation of claim 46, wherein the colloidal silicon dioxide is present in an amount from about 0.1% w/w to about 1.5% w/w.

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.

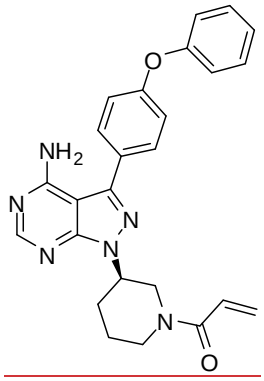
65. The solid tablet formulation of claim 55, wherein the magnesium stearate is present in an amount from about 0.01% w/w to about 2% w/w.

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.