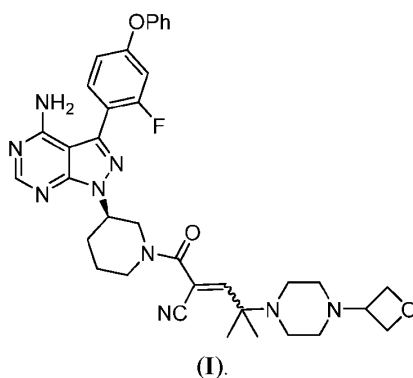


**FORMULATIONS OF 2-[(3R)-2-[4-AMINO-3-(2-FLUORO-4-PHENOXY-PHENYL)PYRAZOLO[3,4-D]PYRIMIDIN-1-YL]PIPERIDINE-1-CARBONYL]-4-METHYL-4[4-(OXETAN-3-YL)PIPERAZIN-1-YL]-PENT-2-ENENITRILE**

**FIELD OF THE DISCLOSURE**

**[0001]** Disclosed herein are novel formulations of 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile, including various solid forms thereof and processes for preparing them. 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile, known as rilzabrutinib, is also referred to herein as the compound of Formula (I), having the structure:



**BACKGROUND**

**[0002]** The compound described by Formula (I) is an inhibitor of Bruton's tyrosine kinase (BTK) and is useful in the treatment of disorders and conditions mediated by BTK activity. BTK is expressed in most hematopoietic cells, including B cells, mast cells, and macrophages. BTK plays a role in the development and activation of B cells and has been implicated in multiple signaling pathways across a wide range of immune-mediated diseases. BTK activity has been implicated in the pathogenesis of several disorders and conditions, such as B cell-related hematological cancers (*e.g.*, non-Hodgkin lymphoma and B cell chronic lymphocytic leukemia) and autoimmune diseases (*e.g.*, rheumatoid arthritis, Sjogren's syndrome, pemphigus, inflammatory bowel disease, lupus, and asthma).

**[0003]** The compound of Formula (I) is disclosed in Example 31 of WO2014/039899. The synthesis of the compound of Formula (I) that is disclosed in WO2014/039899 requires

purification by column chromatography and affords a foam upon removal of solvent, which can be crushed to a powder. Crystalline solid forms characterized as Form A, Form B, and Form C of the compound of Formula (I), as well as processes of preparation thereof, are disclosed in WO2021/150723.

**[0004]** One factor in assessing the suitability of a compound as a therapeutic agent is whether the compound can be administered in a formulation that is easily absorbed by the body and is also shelf stable. The pharmaceutically active substance used to prepare the formulation should have guaranteed stability on long-term storage under various environmental conditions, to prevent the appearance of unintended degradation products in pharmaceutical compositions. Such degradation products may be potentially toxic or result simply in reducing the potency and/or efficacy of the composition.

**[0005]** An additional concern in the large-scale manufacture of pharmaceutical compounds is that the therapeutic substance should be produced by consistent, highly reproducible, manufacturing processes. If an unstable or non-optimized formulation is used, it may result in quality control problems and formulation irregularities. Such a change may affect the reproducibility of the manufacturing process and thus lead to final formulations which do not meet the high quality and stringent requirements imposed on formulations of pharmaceutical compositions. In this regard, it should be generally borne in mind that any modification made to the formulation of a pharmaceutical composition which can improve its physical and chemical stability gives a significant advantage over less stable formulations.

**[0006]** Optimization of the physical properties of a formulation presents another set of challenges that can influence selection of the solid form of the therapeutic agent, the excipients, and the manufacturing process. It is not possible to predict with complete certainty which solid form(s) of a therapeutic agent may possess advantageous physical properties in a particular formulation, such as a tablet, prior to the actual preparation and characterization (both *in vitro* and *in vivo*) of the formulation. It is also not possible to predict how certain excipients might impact the physical properties of a particular formulation, such as a tablet, or affect the processibility of the formulation.

**[0007]** Certain combinations of the solid form of the therapeutic agent and the excipients can impart physical and biological advantages over other combinations. Such advantages, in a non-limiting manner, could include better processability during manufacturing, solubility, or shelf-life stability, just to name a few. In particular, such advantages may include improved flowability, tablet release characteristics, and/or tablet physical properties. The flowability of material during the manufacturing process can be affected by the type and amount of the

therapeutic agent and excipients included in the material. Flowability characteristics can impact the hardness of the tablets, the resistance to tablet crushing, and the pressure needed to compress the material to form tablets. Poor flowability can also result in unacceptable variability in tablet weight.

**[0008]** Another goal in pharmaceutical manufacturing is to limit the number of excipients used in a formulation, which can simplify the manufacturing process and also provide a formulation containing a larger proportion of the therapeutic substance compared to the proportion of excipients. This can be advantageous, for example, to improve patient compliance. Simple, stable formulations that can be manufactured reproducibly and efficiently, and which can provide a tablet with beneficial physical and biological characteristics, are desired.

**[0009]** The present disclosure relates to formulations comprising 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enitrile and at least one pharmaceutically acceptable excipient. For a compound to be suitable for use in a pharmaceutical composition, its formulation should be amenable to large scale manufacturing and isolation, and the physical properties of the formulation should be such that they do not negatively impact the manufacturing process, effectiveness, or cost of the active ingredient. The present disclosure addresses such needs.

## SUMMARY

**[0010]** Disclosed herein are novel formulations of the compound of Formula (I) and processes for preparing the same.

**[0011]** It has been surprisingly found that the solid form of the compound of Formula (I) used in a formulation can affect the flowability and/or physical properties of the formulation. In particular, use of an amorphous solid form of the compound of Formula (I) in a formulation can impart different physical characteristics to a tablet as compared to formulations that contain a crystalline solid form of the compound of Formula (I).

**[0012]** It has also been surprisingly found that certain combinations of excipients used in formulations comprising the compound of Formula (I) can affect the flowability and/or physical properties of formulations that include the compound of Formula (I). In particular, the type and amount of a disintegrant such as croscopolidone, a glidant such as colloidal anhydrous silicon dioxide, a diluent such as microcrystalline cellulose, and/or a lubricant such as magnesium stearate, that is included in the formulation can advantageously affect the characteristics of

tablets containing the compound of Formula (I). Useful methods for producing formulations of the compound of Formula (I), have also been found. The optimized formulations can impart beneficial physical characteristics for formulations of the compounds of Formula (I).

**[0013]** Disclosed herein are formulations that can provide a tablet that includes the compound of Formula (I) or any pharmaceutically acceptable salt thereof, in combination with at least one diluent, at least one disintegrant, at least one lubricant, and optionally, at least one glidant.

**[0014]** Also disclosed are formulations that can provide a tablet that includes the compound of Formula (I) or any pharmaceutically acceptable salt thereof, with the tablet containing about 45% to about 55% by weight of an amorphous solid form of Formula (I), about 35% to about 40% by weight microcrystalline cellulose, about 5% to about 15% by weight crospovidone, and about 0.5% to about 5% by weight sodium stearyl fumarate.

**[0015]** Further disclosed are formulations that can provide a tablet that includes the compound of Formula (I) or any pharmaceutically acceptable salt thereof, with the tablet containing about 60% to about 70% by weight of a crystalline solid form of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide, with the colloidal silicon dioxide being at least one of colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g.

**[0016]** Additionally disclosed are formulations that can provide a tablet comprising at least one compound chosen from the compound of Formula (I) and pharmaceutically acceptable salts thereof, at least one diluent present in an amount ranging from about 10% to about 50% by weight, at least one disintegrant present in an amount ranging from about 0.1% to about 15% by weight, at least one lubricant present in an amount ranging from about 0.01% to about 5% by weight, and optionally, at least one glidant.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0017]** Various aspects of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings of which:

**[0018]** FIG. 1 shows the mean (+SD) plasma concentration-time profiles for rilzabrutinib following single oral administration of two formulations in healthy participants in fasted or fed

conditions (linear scale).

[0019] FIG. 2 shows the mean (+SD) plasma concentration-time profiles for rilzabrutinib following single oral administration of two formulations in healthy participants in fasted or fed conditions (semi-logarithmic scale).

## DETAILED DESCRIPTION

[0020] Reference will now be made in detail to certain embodiments. While the disclosure provides illustrated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the disclosure is intended to cover all alternatives, modifications, and equivalents, which may be included within the disclosure as defined by the appended claims.

[0021] The section headings used herein are for organizational purposes only and are not to be construed as limiting the desired subject matter in any way. In the event that any literature incorporated by reference contradicts any term defined in this specification, this specification controls. While the present teachings are described in conjunction with various embodiments, it is not intended that the present teachings be limited to such embodiments. On the contrary, the present teachings encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

### Definitions

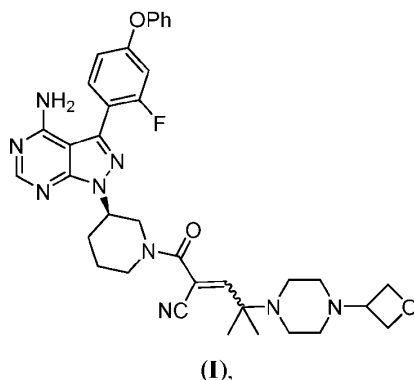
[0022] Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this disclosure and have the following meaning.

[0023] As used herein, “a” or “an” entity refers to one or more of that entity, *e.g.*, “a compound” refers to one or more compounds or at least one compound unless stated otherwise. As such, the terms “a” (or “an”), “one or more” and “at least one” are used interchangeably herein.

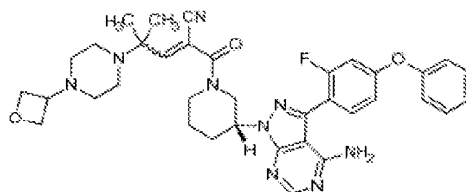
[0024] As used herein, the term “about” means approximately, in the region of, roughly or around. When the term “about” is used in conjunction with a numerical range it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 5%. In certain embodiments, the term “about” indicates the designated value  $\pm$  10%,  $\pm$  5%, or  $\pm$  1 %. In certain embodiments, where applicable, the term “about” indicates the designated value(s)  $\pm$  one standard deviation of that value(s).

[0025] The term “and/or” is used in this disclosure to mean either “and” or “or” unless indicated otherwise.

[0026] As used herein, “2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile”, “rilzabrutinib” and “the compound of Formula (I),” are used interchangeably to refer to a compound having the following structure:



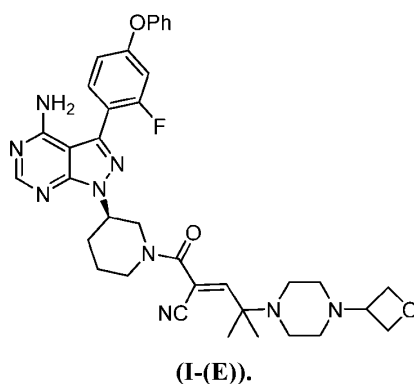
which is also known as: 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]-(E and Z)-pent-2-enenitrile; (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; 1-piperidinepropanenitrile, 3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]- $\alpha$ -[2-methyl-2-[4-(3-oxetanyl)-1-piperazinyl]propylidene]- $\beta$ -oxo-, (3R)-; (EZ)-2-[(3R)-3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile; and also by the International Nonproprietary Names for Pharmaceutical Substances (INN) as published by the World Health Organization ([https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-\(inn\)/pl121.pdf?sfvrsn=69617906\\_15&download=true](https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/pl121.pdf?sfvrsn=69617906_15&download=true)) having the following structure:



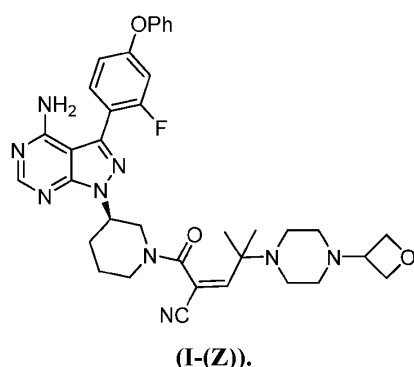
The compound of Formula (I) includes E and Z isomers, as indicated by the wavy bond in the structure shown above. The compound of Formula (I) may be present as a salt form.

[0027] In some embodiments, the compound of Formula (I) is a compound of Formula (I-E), the E isomer of the compound of Formula (I). In some embodiments, the compound of

Formula (I-(E)) has the following structure:



**[0028]** In some embodiments, the compound of Formula (I) is a compound of Formula (I-(Z)), the Z isomer of the compound of Formula (I). In some embodiments, the compound of Formula (I-(Z)) has the following structure:



**[0029]** In some embodiments, the compound of Formula (I) comprises a compound of Formula (I-(Z)). In some embodiments, the compound of Formula (I) comprises a compound of Formula (I-(E)). In some embodiments, the compound of Formula (I) comprises a mixture of a compound of Formula (I-(Z)) and a compound of Formula (I-(E)).

**[0030]** A dose of the (E) isomer of the compound of Formula (I) may contain the corresponding (Z) isomer in less than about 10% by weight, such as less than about 5% by weight, less than about 2% by weight, and less than about 1% by weight. When the compound of Formula (I) is denoted as a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enitrile, it means that the amount of (E) or (Z) isomer in the mixture is greater than about 2% by weight. In some embodiments, when the compound of Formula (I) is denoted as a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-

yl)piperazin-1-yl]pent-2-enenitrile, it means that the amount of (Z) isomer in the mixture is equal to or less than about 10% by weight, such as equal to or less than about 5% by weight, equal to or less than about 2% by weight, or equal to or less than about 1% by weight.

**[0031]** A dose of the (Z) isomer of the compound of Formula (I) may contain the corresponding (E) isomer in less than about 10% by weight, such as less than about 5% by weight, less than about 2% by weight, and less than about 1% by weight. In some embodiments, when the compound of Formula (I) is denoted as a mixture of (E) and (Z) isomers of (R)-2-[3-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4-[4-(oxetan-3-yl)piperazin-1-yl]pent-2-enenitrile, it means that the amount of (E) isomer in the mixture is equal to or less than about 10% by weight, such as equal to or less than about 5% by weight, equal to or less than about 2% by weight, or equal to or less than about 1% by weight.

**[0032]** In some embodiments, the molar ratio of the (E) to (Z) isomer of the compound of Formula (I) is 8:2. In some embodiments, the molar ratio of the (E) to (Z) isomer of the compound of Formula (I) is 9:1. In some embodiments, the molar ratio of the (E) to (Z) isomer of the compound of Formula (I) is 98:2. In some embodiments, the molar ratio of the (E) to (Z) isomer of the compound of Formula (I) is 99:1.

**[0033]** The compound of Formula (I) may also exist in a salt form, in other words in the form of an ionic combination with one or more cation or anion. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

**[0034]** A “pharmaceutically acceptable salt” of the compound of Formula (I), as used herein means an acid addition salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the compound from which the salt is made. Such salts include salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, and the like.

**[0035]** As used herein, a “pharmaceutically acceptable excipient” refers to a carrier or an excipient that is useful in preparing a pharmaceutical composition. For example, a pharmaceutically acceptable excipient is generally safe and includes carriers and excipients that

are generally considered acceptable for mammalian pharmaceutical use.

**[0036]** As used herein, the term “crystalline” or “crystalline solid form,” refers to a solid form which is substantially free of any amorphous solid-state form.

**[0037]** In some embodiments, “substantially free” means less than about 10 % w/w, less than about 9 % w/w, less than about 8 % w/w, less than about 7 % w/w, less than about 6 % w/w, less than about 5 % w/w, less than about 4 % w/w, less than about 3 % w/w, less than about 2.5 % w/w, less than about 2 % w/w, less than about 1.5 % w/w, less than about 1 % w/w, less than about 0.75 % w/w, less than about 0.50 % w/w, less than about 0.25 % w/w, less than about 0.10 % w/w, or less than about 0.05 % w/w of other crystalline forms of the compound and the amorphous compound. In some embodiments, “substantially free” means an undetectable amount of other crystalline forms of the compound and the amorphous compound.

**[0038]** As used herein, the term “substantially pure” or “substantially crystalline” means that the crystalline form contains at least 90 percent, for example at least 95 percent, such as at least 97 percent, and even at least 99 percent by weight of the indicated crystalline form compared to the total weight of the compound of all forms.

**[0039]** Alternatively, it will be understood that “substantially pure” or “substantially crystalline” means that the crystalline form contains less than 10 percent, for example less than 5 percent, such as less than 3 percent, and even less than 1 percent by weight of impurities, including other polymorphic or amorphous forms compared to the total weight of the compound of all forms.

**[0040]** As used herein, the term “amorphous” refers to a solid material having no long-range order in the position of its molecules. Amorphous solids are generally supercooled liquids in which the molecules are arranged in a random manner so that there is no well-defined arrangement, *e.g.*, molecular packing, and no long-range order. For example, an amorphous material is a solid material having no sharp characteristic signal(s) in its X-ray power diffractogram (*i.e.*, is not crystalline as determined by XRPD). Instead, one or more broad peaks (*e.g.*, halos) appear in its diffractogram. Broad peaks are characteristic of an amorphous solid.

**[0041]** As used herein, the term “substantially amorphous” refers to a solid material having little or no long-range order in the position of its molecules. For example, substantially amorphous materials have less than 15% crystallinity (*e.g.*, less than 10% crystallinity or less than 5% crystallinity). “Substantially amorphous” includes the descriptor “amorphous,” which refers to materials having no (0%) crystallinity.

**[0042]** A “therapeutically effective amount” means the amount of the BTK inhibitor compound, that, when administered to a mammal for treating a disease, is sufficient to effect

such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, species, etc., of the mammal to be treated. For example, the mammal to be treated may be a human. In an embodiment, the term “therapeutically effective amount” means the amount of the BTK inhibitor compound, that, when administered to a human for treating a disease, is sufficient to effect such treatment for the disease.

**[0043]** As used herein, the term “treat”, “treating” or “treatment”, when used in connection with a disorder or condition, includes any effect *e.g.*, lessening, reducing, modulating, ameliorating, or eliminating, that results in improvement of the disorder or condition. Improvements in or lessening the severity of any symptom of the disorder or condition can be readily assessed according to standard methods and techniques known in the art.

**[0044]** As used herein, the term “XRPD” refers to the analytical characterization method of X-ray powder diffraction. XRPD patterns can be recorded at ambient conditions in transmission or reflection geometry using a diffractometer.

**[0045]** As used herein, the terms “comprising” and “including” can be used interchangeably. The terms “comprising” and “including” are to be interpreted as specifying the presence of the stated features or components as referred to, but does not preclude the presence or addition of one or more features, or components, or groups thereof. Additionally, the terms “comprising” and “including” are intended to include examples encompassed by the term “consisting of”. Consequently, the term “consisting of” can be used in place of the terms “comprising” and “including” to provide for more specific embodiments of the compounds and/or methods disclosed herein.

**[0046]** The term “consisting of” means that a subject-matter has at least 90%, 95%, 97%, 98% or 99% of the stated features or components of which it consists. In another embodiment the term “consisting of” excludes from the scope of any succeeding recitation any other features or components, excepting those that are not essential to the technical effect to be achieved.

**[0047]** As used herein, the term “or” is to be interpreted as an inclusive “or” meaning any one or any combination. Therefore, “A, B or C” means any of the following: “A; B; C; A and B; A and C; B and C; A, B and C”. An exception to this definition will occur only when a combination of elements, functions, steps or acts are in some way inherently mutually exclusive.

**[0048]** In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer),

unless otherwise indicated. Also, any number range recited herein relating to any physical feature, such as polymer subunits, size, or thickness, are to be understood to include any integer within the recited range, unless otherwise indicated. As used herein, the terms “about” and “approximately” mean  $\pm 10\%$ ,  $\pm 5\%$ , or  $\pm 1\%$  of the indicated range, value, or structure, unless otherwise indicated.

[0049] It should be noted that if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0050] Although various features of the compounds and methods disclosed herein may be described in the context of a single embodiment, the features may also be provided separately or in any suitable combination. Conversely, although the compounds and methods disclosed herein may be described in the context of separate embodiments for clarity, the compounds and methods disclosed herein may also be implemented in a single embodiment.

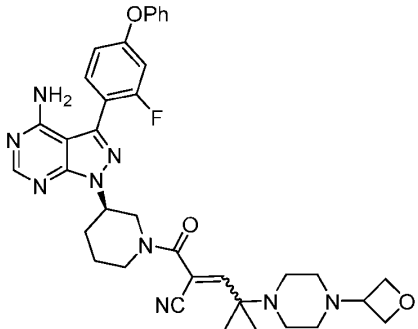
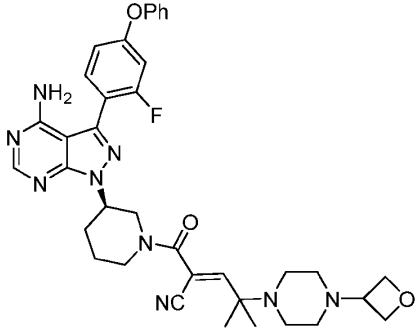
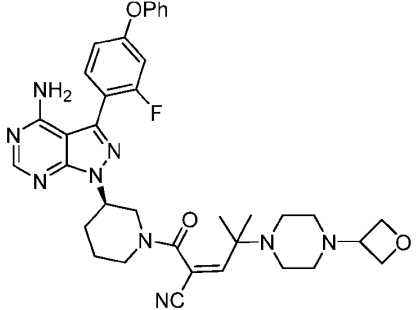
#### **Solid Forms of the Compound of Formula (I)**

[0051] The BTK inhibitor compound can be prepared according to the methods and schemes described in, for example, WO2014/039899. In addition, it can be prepared as described in WO2021/150723.

[0052] In some embodiments, provided herein is a solid form of a compound of Formula (I), or a salt thereof. In some embodiments, provided is a salt of a compound selected from the compounds in Table 1. In some embodiments, provided is a crystalline form of a compound selected from the compounds in Table 1, or a salt thereof. In some embodiments, provided is crystalline Form B of a compound selected from the compounds in Table 1, or a salt thereof. In some embodiments, provided is an amorphous form of a compound selected from the compounds in Table 1, or a salt thereof.

[0053] Although certain compounds described in the present disclosure, including in Table 1, are presented as specific stereoisomers and/or in a non-stereochemical form, it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of the compounds of the present disclosure, including in Table 1, are herein described.

Table 1.

| Compound of<br>Formula No. | Structure                                                                            |
|----------------------------|--------------------------------------------------------------------------------------|
| <b>I</b>                   |    |
| <b>I-(E)</b>               |   |
| <b>I-(Z)</b>               |  |

or a salt thereof.

**[0054]** Solid forms of the compound of Formula (I) include crystalline Form A, crystalline Form B, and crystalline Form C, and any salts thereof.

**[0055]** Crystalline Form A of the compound of formula (I) can be identified and/or characterized by various characteristics, including upon analysis by differential scanning calorimetry (DSC), thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR), and X-ray powder diffraction (XRPD).

[0056] In some embodiments, crystalline Form A of the compound of formula (I) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 146 °C to about 147 °C. In some embodiments, crystalline Form A of the compound of formula (I) is characterized by a DSC thermogram showing onset of melting/decomposition at about 140.6 °C to about 141.2 °C. In some embodiments, crystalline Form A of the compound of formula (I) is characterized by a DSC thermogram showing onset of melting at about 140.6 °C to about 141.2 °C. In some embodiments, the associated enthalpy is about 52 J/g ( $\Delta H = 52$  J/g).

[0057] In some embodiments, crystalline Form A of the compound of formula (I) is characterized by a mass loss of less than 1.0 wt. % between 25 °C and 200 °C by thermogravimetric analysis. In some embodiments, this mass loss corresponds to loss of isopropyl acetate, which is released around the melting temperature. In some embodiments, decomposition is observed at higher temperatures (onset at about 220 °C to about 230 °C). In some embodiments, crystalline Form A of the compound of formula (I) is characterized by a water content of less than 1% upon storage at 95% relative humidity (RH).

[0058] In some embodiments, crystalline Form A of the compound of formula (I) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu K $\alpha$  radiation, having a signal at at least three two-theta values chosen from  $5.6 \pm 0.2$ ,  $12.7 \pm 0.2$ ,  $16.5 \pm 0.2$ ,  $17.0 \pm 0.2$ ,  $17.7 \pm 0.2$ ,  $18.7 \pm 0.2$ ,  $19.2 \pm 0.2$ ,  $20.7 \pm 0.2$ ,  $22.2 \pm 0.2$ , and  $24.4 \pm 0.2$ .

[0059] Crystalline Form B of the compound of formula (I) can be identified and/or characterized by various characteristics, including upon analysis by differential scanning calorimetry (DSC), thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR), and X-ray powder diffraction (XRPD).

[0060] In some embodiments, crystalline Form B of the compound of formula (I) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 141 °C to about 142 °C. In some embodiments, crystalline Form B of the compound of formula (I) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 144 °C to about 146 °C. In some embodiments, crystalline Form B of the compound of formula (I) is characterized by a DSC thermogram showing onset of melting at about 131.8 °C to about 132.4 °C. In some embodiments, crystalline Form B of the compound of formula (I) is characterized by a DSC thermogram showing onset of melting at about 139.3 °C. In some embodiments, crystalline Form B of the compound of formula (I) is characterized by a water content of less than 1.3% upon storage at 95% relative humidity (RH). In some embodiments, the associated enthalpy is about 54.9 J/g ( $\Delta H = 54.9$  J/g).

**[0061]** In some embodiments, crystalline Form B of the compound of formula (I) is characterized by a mass loss of less than 0.8 wt. % between 25 °C and 162 °C by thermogravimetric analysis. In some embodiments, in addition to the above mass loss, there is a further mass loss of less than 0.8 wt. % between 162 °C and 250 °C by thermogravimetric analysis. In some embodiments, this further mass loss corresponds to removal of ethyl acetate. In some embodiments, decomposition is observed at higher temperatures (onset at about 250 °C to about 253 °C).

**[0062]** In some embodiments, crystalline Form B of the compound of formula (I) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu K $\alpha$  radiation with signals at at least three two-theta values chosen from  $10.8 \pm 0.2$ ,  $15.3 \pm 0.2$ ,  $16.3 \pm 0.2$ ,  $17.9 \pm 0.2$ ,  $18.4 \pm 0.2$ ,  $18.7 \pm 0.2$ ,  $22.0 \pm 0.2$ , and  $22.9 \pm 0.2$ .

**[0063]** Crystalline Form C of the compound of formula (I) can be identified and/or characterized by various characteristics, including upon analysis by differential scanning calorimetry (DSC), thermogravimetry coupled to Fourier transform infrared spectroscopy (TG-FTIR), and X-ray powder diffraction (XRPD).

**[0064]** In some embodiments, crystalline Form C of the compound of formula (I) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 118.5 °C to about 119 °C, wherein the DSC scanning rate is 15 °C/min. In some embodiments, crystalline Form C of the compound of formula (I) is characterized by a DSC thermogram showing an onset of melting at about 115.6 °C to about 116.0 °C, wherein the DSC scanning rate is 15 °C/min. In some embodiments, crystalline Form C of the compound of formula (I) is characterized by a DSC thermogram having a peak endotherm (melting temperature) at about 120.5 °C to about 121 °C, wherein the DSC scanning rate is 10 °C/min. In some embodiments, crystalline Form C of the compound of formula (I) is characterized by a DSC thermogram showing onset of melting/decomposition at about 118.0 °C to about 118.5 °C, wherein the DSC scanning rate is 10 °C/min.

**[0065]** In some embodiments, crystalline Form C is characterized by a TGA thermal curve having a mass loss of less than 5% between 25 °C and 150 °C. In some embodiments, crystalline Form C is characterized by a mass loss of less than 5 wt. % between 25 °C and 145 °C. In some embodiments, the mass loss is due to removal of acetonitrile.

**[0066]** In some embodiments, crystalline Form C of the compound of formula (I) is characterized by an X-ray powder diffractogram generated by an X-ray powder diffraction analysis with an incident beam of Cu K $\alpha$  radiation with signals at at least three two-theta values

chosen from  $9.8 \pm 0.2$ ,  $10.2 \pm 0.2$ ,  $15.6 \pm 0.2$ ,  $16.6 \pm 0.2$ ,  $18.6 \pm 0.2$ ,  $18.9 \pm 0.2$ ,  $19.6 \pm 0.2$ , and  $21.6 \pm 0.2$ .

#### **Formulations and Processes for their Preparation**

[0067] In accordance with the current disclosure, the compound of Formula (I) can be incorporated into a formulation prepared by one or more of the following processes. The processes described herein can be combined in any suitable order, as would be understood by a person of skill in the relevant art.

##### **[0068] Solid Formulations**

[0069] Disclosed herein are tablets that include a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0070] In some embodiments, the tablet includes at least one compound chosen from the compound of Formula (I) or a pharmaceutically acceptable salt thereof, with at least one diluent, at least one disintegrant, at least one lubricant, and optionally, at least one glidant. In some embodiments, the tablet includes at least one compound chosen from the compound of Formula (I) or a pharmaceutically acceptable salt thereof, with at least one diluent, at least one disintegrant, and at least one lubricant.

[0071] In some embodiments, the tablet includes an intragranular phase and an extragranular phase. In some embodiments, the tablet includes two phases. In some embodiments, the tablet includes at least two phases. In some embodiments, the tablet includes at least two phases and a film coating.

[0072] In some embodiments, the tablet includes at least one diluent that is chosen from lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, calcium phosphate, hydroxypropylmethylcellulose, sucrose, calcium sulfate, calcium lactate, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, kaolin, sodium chloride, inositol, and bentonite. The diluent can be microcrystalline cellulose, such as microcrystalline cellulose 50  $\mu\text{m}$ , microcrystalline cellulose 180  $\mu\text{m}$ , or both. The diluent may be present in the tablet in a total amount ranging from about 75 mg to about 400 mg. The diluent may be present in a total amount ranging from about 10% to about 50% by weight of the tablet. The diluent may be present in the tablet in the intragranular phase in a total amount ranging from about 15% to about 45% by weight. The diluent may be present in the extragranular phase in a total amount ranging from about 0% to about 15% by weight.

[0073] In some embodiments, the tablet includes at least one glidant that is chosen from colloidal silicon dioxide and talc. The glidant can be a mixture of colloidal silicon dioxide

having an average specific surface area of about 200 m<sup>2</sup>/g and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g. The glidant can include colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g, colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g, or both. The glidant may be present in the tablet in a total amount ranging from 0 mg to about 50 mg. The glidant may be present in a total amount ranging from about 0% to about 5% by weight of the tablet. The glidant may be present in the tablet in the intragranular phase in a total amount ranging from about 0% to about 5% by weight. The glidant may be present in the extragranular phase of the tablet in a total amount ranging from about 0% to about 5% by weight.

**[0074]** In some embodiments, the tablet includes at least one disintegrant that is chosen from a starch, a cross-linked starch, a cellulose, a cross-linked cellulose, a cross-linked polymer, an alginate, a clay, a gum, a glycolate, bentonite, a natural sponge, a surfactant, a resin, citrus pulp, and sodium lauryl sulfate. The disintegrant can include cross linked polyvinyl N-pyrrolidone (crospovidone) and cross linked carboxymethyl cellulose (croscarmellose). The disintegrant can include cross linked polyvinyl N-pyrrolidone (crospovidone), cross linked carboxymethyl cellulose (croscarmellose), or both crospovidone and croscarmellose. The disintegrant may be present in a total amount in the tablet ranging from 1 mg to about 125 mg. The disintegrant may be present in a total amount in the tablet ranging from about 0.1% to about 15% by weight of the tablet. The disintegrant may be present in the intragranular phase of the tablet in a total amount ranging from about 0.1% to about 10% by weight. The disintegrant may be present in the extragranular phase of the tablet in a total amount ranging from about 0% to about 10% by weight.

**[0075]** In some embodiments, the tablet includes at least one lubricant that is chosen from stearic acid, calcium hydroxide, talc, a hydrocarbon, a hydrogenated vegetable oil, higher fatty acids, a stearate, glycerol, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol, a methoxypolyethylene glycol, sodium oleate, sodium benzoate, glyceryl behenate, magnesium or sodium lauryl sulfate, colloidal silica, a starch, silicone oil, and a surfactant. The at least one lubricant may be chosen from magnesium stearate and sodium stearyl fumarate. The at least one lubricant may be chosen from magnesium stearate, sodium stearyl fumarate, or both. The at least one lubricant may be magnesium stearate. The at least one lubricant may be sodium stearyl fumarate. The lubricant may be present in the tablet in a total amount ranging from 0.1 mg to about 50 mg. The lubricant may be present in a total amount ranging from about 0.01% to about 5% by weight of the tablet. The lubricant is present in the intragranular phase of the tablet in a total amount ranging from about

0.1% to about 5% by weight. The lubricant may be present in the extragranular phase of the tablet in a total amount ranging from about 0% to about 5% by weight.

**[0076]** In some embodiments, the tablet includes an intragranular phase that contains at least one diluent, at least one disintegrant, and at least one lubricant. The diluent in the intragranular phase of the tablet may be microcrystalline cellulose 50  $\mu\text{m}$ . The lubricant in the intragranular phase of the tablet may be magnesium stearate. The lubricant in the intragranular phase of the tablet may be sodium stearyl fumarate. The disintegrant in the intragranular phase of the tablet may be cross linked polyvinyl N-pyrrolidone (crospovidone). The intragranular phase of the tablet may further include at least one glidant. The glidant in the intragranular phase of the tablet may be colloidal silicon dioxide having an average specific surface area of about 200  $\text{m}^2/\text{g}$ , or it may be colloidal silicon dioxide having an average specific surface area of about 300  $\text{m}^2/\text{g}$ .

**[0077]** In some embodiments, the tablet includes an extragranular phase that contains at least one lubricant. The lubricant in the extragranular phase of the tablet may be magnesium stearate. The lubricant in the extragranular phase of the tablet may be sodium stearyl fumarate. The extragranular phase of the tablet may further include at least one diluent. The diluent in the extragranular phase of the tablet may be microcrystalline cellulose 180  $\mu\text{m}$ . The extragranular phase of the tablet may further include at least one glidant. The glidant in the extragranular phase of the tablet may be colloidal silicon dioxide having an average specific surface area of about 200  $\text{m}^2/\text{g}$ , or it may be colloidal silicon dioxide having an average specific surface area of about 300  $\text{m}^2/\text{g}$ . The extragranular phase of the tablet may further include at least one disintegrant. The disintegrant in the extragranular phase of the tablet may be cross linked polyvinyl N-pyrrolidone (crospovidone).

**[0078]** In some embodiments, the compound of Formula (I) that is present in the tablet is a solid form that is at least 50% crystalline, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, 99.5%, or 100% crystalline. The compound of Formula (I) that is present in the tablet may be present in an amount ranging from about 200 mg to about 650 mg. The compound of Formula (I) that is present in the tablet may be present in an amount of about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590

mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, or about 650 mg. For example, the compound of Formula (I) may be present in the tablet in an amount of about 300 mg. Alternatively, the compound of Formula (I) may be present in the tablet in an amount of about 500 mg. Alternatively, the compound of Formula (I) may be present in the tablet in an amount of about 600 mg. The compound of Formula (I) present in the tablet may be present in an amount of about 40% to about 75% by weight of the tablet. For example, the compound of Formula (I) may be present in an amount of about 50% by weight of the tablet. Alternatively, the compound of Formula (I) may be present in the tablet in an amount of about 65% by weight of the tablet.

**[0079]** In some embodiments, the tablet that includes a compound of Formula (I) also includes at least one coating layer. The coating layer may include a taste masking agent. The weight of the coating layer may be included in the total weight of the tablet. Alternatively, the weight of the tablet may not include the weight of the coating layer.

**[0080]** In other embodiments, the tablet includes about 60% to about 70% by weight of the tablet of crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight of the tablet of microcrystalline cellulose, about 0.5% to about 5% by weight of the tablet of crospovidone, about 0.1% to about 5% by weight of the tablet of magnesium stearate, and about 0.1% to about 5% by weight of the tablet of colloidal silicon dioxide.

**[0081]** In some embodiments, the tablet that includes the compound of Formula (I) has an intragranular phase and an extragranular phase. The compound of Formula (I) may be present in the intragranular phase of the tablet. The compound of Formula (I) may be present in at least one of the intragranular phase or the extragranular phase of the tablet.

**[0082]** In further embodiments, the tablet has an intragranular phase that includes about 65% by weight of the tablet of the compound of Formula (I), about 31% by weight of the tablet of microcrystalline cellulose, about 2% by weight of the tablet of crospovidone, about 0.25% by weight of the tablet of magnesium stearate, and about 1% by weight of the tablet of colloidal silicon dioxide. In some embodiments, the tablet has an extragranular phase that includes about 1% by weight of the tablet of magnesium stearate.

**[0083]** In some embodiments, the tablet has the compound of Formula (I) present in the tablet in an amorphous solid form. The tablet may have the compound of Formula (I) present in the tablet in crystalline solid form. The tablet may have the compound of Formula (I) present in the tablet in a crystalline form that is at least one of crystalline Form A, Form B, and Form C. The crystalline form of the compound of Formula (I) present in the tablet may be Form A. The crystalline form of the compound of Formula (I) present in the tablet may be Form B. The

crystalline form of the compound of Formula (I) present in the tablet may be Form C.

**[0084]** In further embodiments, the tablet includes about 45% to about 55% by weight of the tablet of amorphous compound of Formula (I), about 35% to about 40% by weight of the tablet of microcrystalline cellulose, about 5% to about 15% by weight of the tablet of crospovidone, and about 0.5% to about 5% by weight of the tablet of sodium stearyl fumarate.

**[0085]** The intragranular phase of the tablet may include about 50% by weight of the compound of Formula (I), about 38% by weight microcrystalline cellulose, about 10% by weight crospovidone, and about 2% by weight sodium stearyl fumarate. The extragranular phase of the tablet may include about 5% by weight crospovidone and about 1% by weight sodium stearyl fumarate.

**[0086]** In additional embodiments, the tablet has the compound of Formula (I) present in the tablet in an amount of about 270 mg. The tablet may include the compound of Formula (I) in an amount of about 300 mg or about 400 mg. The tablet may include the compound of Formula (I) in an amount of about 300 mg. The tablet may include the compound of Formula (I) in an amount of about 400 mg. The compound of Formula (I) present in the tablet may be present in an amount of about 400 mg or about 450 mg. The compound of Formula (I) present in the tablet may be present in an amount of about 450 mg. The compound of Formula (I) may be present in the tablet in an amount of about 500 mg. The compound of Formula (I) may be present in the tablet in an amount of about 550 mg. The compound of Formula (I) may be present in the tablet in an amount of about 600 mg. The compound of Formula (I) may be present in the tablet in an amount of about 650 mg.

**[0087]** In additional embodiments, the tablet includes about 60% to about 70% by weight of the tablet of crystalline Form B of the compound of Formula (I), about 20% to about 35% by weight of the tablet of microcrystalline cellulose, about 0.5% to about 10% by weight of the tablet of disintegrant, about 0.1% to about 5% by weight of the tablet of magnesium stearate, and about 0.1% to about 5% by weight of the tablet of colloidal silicon dioxide. The tablet may include a disintegrant that includes at least one of crospovidone and croscarmellose.

**[0088]** The intragranular phase of the tablet may include about 65% by weight of the tablet of the compound of Formula (I), about 23% to about 31% by weight of the tablet of microcrystalline cellulose, about 2.0% to about 4.0% by weight of the tablet of disintegrant, about 0.5% to about 1.0% by weight of the tablet of magnesium stearate, and about 0.9% by weight of the tablet of colloidal silicon dioxide. The extragranular phase of the tablet may include about 1.5% by weight of the tablet of microcrystalline cellulose, about 0% to about 2.0% by weight of the tablet of disintegrant, about 0.2% to about 1.0% by weight of the tablet of

magnesium stearate, and about 0.4% by weight of the tablet of colloidal silicon dioxide.

**[0089]** In yet additional embodiments, the tablet includes about 60% to about 70% by weight of the tablet of crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight of the tablet of microcrystalline cellulose, about 0.5% to about 5% by weight of the tablet of crospovidone, about 0.1% to about 5% by weight of the tablet of magnesium stearate, and about 0.1% to about 5% by weight of the tablet of colloidal silicon dioxide.

**[0090]** The intragranular phase may include about 65% by weight of the of the tablet of the compound of Formula (I), about 31% by weight of the tablet of microcrystalline cellulose, about 2.0% by weight of the tablet of crospovidone, about 0.25% by weight of the tablet of magnesium stearate, and about 0.9% by weight of the tablet of colloidal silicon dioxide. The extragranular phase may include about 1.0% by weight of the tablet of magnesium stearate and about 0.4% by weight of the tablet of colloidal silicon dioxide.

**[0091]** In further additional embodiments, the tablet includes about 60% to about 70% by of the tablet of weight crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight of the tablet of microcrystalline cellulose, about 0.5% to about 5% by weight of the tablet of crospovidone, about 0.1% to about 5% by weight of the tablet of magnesium stearate, and about 0.1% to about 5% by weight of the tablet of colloidal silicon dioxide.

**[0092]** The intragranular phase of the tablet may include about 65% by weight of the tablet of the compound of Formula (I), about 30% by weight of the tablet of microcrystalline cellulose, about 2.0% by weight of the tablet of crospovidone, about 0.5% by weight of the tablet of magnesium stearate, and about 0.9% by weight of the tablet of colloidal silicon dioxide. The extragranular phase of the tablet may include about 1.0% by weight of the tablet of magnesium stearate and about 0.4% by weight of the tablet of colloidal silicon dioxide.

**[0093]** In additional embodiments, the tablet includes about 60% to about 70% by weight of the tablet of a crystalline compound of Formula (I), about 25% to about 35% by weight of the tablet of microcrystalline cellulose, about 0.5% to about 5% by weight of the tablet of crospovidone, about 0.1% to about 5% by weight of the tablet of magnesium stearate, and about 0.1% to about 5% by weight of the tablet of colloidal silicon dioxide. The colloidal silicon dioxide can include at least one of colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g. The colloidal silicon dioxide be colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g. The colloidal silicon dioxide can be colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g.

[0094] The intragranular phase of the tablet can include about 65% by weight of the tablet of a crystalline solid form of the compound of Formula (I), about 20% to about 30% by weight of the tablet of microcrystalline cellulose, about 2.0% by weight of the tablet of crospovidone, about 0.25% by weight of the tablet of magnesium stearate, and about 0.7 to about 0.9% by weight of the tablet of colloidal silicon dioxide. The extragranular phase of the tablet can include about 1.0% by weight of the tablet of magnesium stearate, about 0% to about 10% by weight of the tablet of microcrystalline cellulose, and about 0.4% to about 0.6% by weight of the tablet of colloidal silicon dioxide.

[0095] In additional embodiments, the tablet comprising the compound of Formula (I) includes a film-coating agent. The film coating may be present in an amount of about 2% to about 5% by weight, relative to the total weight of the tablet. The film coating may be present in an amount of about 3% relative to the total weight of the tablet. The weight of the film-coating layer may be included in the total weight of the tablet. Alternatively, the weight of the tablet may not include the weight of the film coating agent.

[0096] The tablet that includes a compound of Formula (I) or a pharmaceutically acceptable salt thereof, may be used in a method of treating a disease or condition mediated by BTK in a patient in need thereof. The method of treating a disease or condition mediated by BTK in a patient in need thereof may include administering to the patient a tablet that includes a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[0097] Diseases or conditions that may be mediated by BTK in a patient, may be selected from at least one of acne, allergy, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson syndrome, toxic epidermal necrolysis (TEN), pemphigus vulgaris, pemphigus foliaceus, ankylosing spondylitis, antiphospholipid antibody syndrome, vasculitis, Guillain-Barre syndrome, scleroderma, Wegener's granulomatosis, psoriasis, granulomatosis with polyangiitis, thrombotic thrombocytopenic purpura, polyarteritis nodosa, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, asthma, moderate-to-severe asthma, mild asthma, moderate asthma, severe asthma, asthma that is not well controlled, autoimmune hepatitis, Behcet's disease, Grave's disease, nephritis, pancreatitis, primary biliary cirrhosis, ulcerative colitis, colitis, conjunctivitis, dermatitis, atopic dermatitis, drug eruptions, drug-induced thrombocytopenia (DITP), vaccine-induced thrombosis and thrombocytopenia (VITT), eczema, folliculitis decalvans, pseudofolliculitis barbae, leucoclastic vasculitis, hidradenitis suppurativa, palmar plantar pustulosis, Lichenoid dermatitis, mycosis fungoides, sweet syndrome, follicular lymphoma, diffuse large B cell lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia,

B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom 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, non-Hodgkin lymphoma, warm autoimmune hemolytic anemia (wAIHA), B-cell acute lymphoblastic leukemia (B-ALL), small lymphocytic lymphoma (SLL), intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, B-cell non-Hodgkin lymphoma, idiopathic thrombocytopenic purpura, IgG4-related diseases (IgG4-RD) and flares thereof, antiphospholipid syndrome (APS), membranous nephropathy (MN), immune thrombocytopenia, inflammatory bowel disease, itch associated with atopic dermatitis, lupus, cutaneous lupus, cutaneous lupus erythematosus, lupus nephritis, mixed connective tissue disease, multiple myeloma, multiple sclerosis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), sepsis, sepsis induced acute lung injury, diffuse alveolar damage (DAD), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (SHIH), cytokine release syndrome (CRS), cutaneous form of systemic sclerosis (CREST), cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, urticaria, chronic spontaneous urticaria (CSU), chronic idiopathic urticaria (CIU), AI urticaria, and IgA nephropathy.

**[0098]** The tablet that includes a compound of Formula (I) or a pharmaceutically acceptable salt thereof, may be used for treating a disease or condition mediated by the BTK receptor. The method of treating a disease or condition mediated by the BTK receptor may include administering to a patient a tablet that includes a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

**[0099]** Solid formulations can include ranges of components such as shown in Table 2, below:

Table 2: Components of Exemplary Formulations

| <b>component</b>  | <b>amount per tablet<br/>(wt %); range</b> | <b>approx. amount per<br/>tablet (wt); range</b> |
|-------------------|--------------------------------------------|--------------------------------------------------|
| API/rilzabrutinib | 50% - 65%                                  | 200 mg – 650 mg                                  |
| diluent           | 10% - 50%                                  | 75 mg – 400 mg                                   |
| disintegrant      | 0.1% - 15%                                 | 1 mg – 125 mg                                    |
| lubricant         | 0.01% - 5%                                 | 0.1 mg – 50 mg                                   |
| glidant           | 0% - 5%                                    | 0 mg – 50 mg                                     |
| binder            | 0% - 5%                                    | 0 mg – 50 mg                                     |

**[00100]** In some embodiments, the compound of Formula (I) is present in at least 50% crystalline form, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, 99.5%, or 100% crystalline. In some embodiments, the compound of Formula (I) is present in an amorphous form. In some embodiments, the compound of Formula (I) is present in a crystalline form. In some embodiments, the compound of Formula (I) is present as crystalline Form B.

**[00101]** The compound of Formula (I) can be present in a tablet in a total amount ranging from about 40% by weight to about 75% by weight of the tablet. In some embodiments, the compound of Formula (I) is present in a tablet in a total amount ranging from about 50% by weight to about 65% by weight of the tablet. In some embodiments, the compound of Formula (I) is present in a tablet in a total amount of about 50% by weight. In some embodiments, the compound of Formula (I) is present in a tablet in a total amount of about 65% by weight. In some embodiments, the compound of Formula (I) is present in an amorphous form in a total amount of about 50% by weight of the tablet. In some embodiments, the compound of Formula (I) is present in a crystalline form in a total amount of about 65% by weight of the tablet. In some embodiments, the compound of Formula (I) is present in crystalline Form B in a total amount of about 65% by weight of the tablet.

**[00102]** In some embodiments, the tablet includes the compound of Formula (I) in an amount ranging from about 200 mg to about 650 mg. In some embodiments, the compound of Formula (I) is present in an amount of about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, or about 650 mg. In some embodiments, the compound of Formula (I) is present in an amount of about 300 mg. In some embodiments, the compound of Formula (I) is present in an amount of about 500 mg. In some embodiments, the compound of Formula (I) is present in an amount of about 550 mg. In some embodiments, the compound of Formula (I) is present in an amount of about 600 mg. In some embodiments, the compound of Formula (I) is present in an amount of about 650 mg.

**[00103]** Diluents are chemical compounds that are used to dilute the compound of interest prior to delivery. Diluents can also be used to stabilize compounds because they can provide a

more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In some embodiments, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include *e.g.*, lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel®; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac® (Amstar); hydroxypropyl-methylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

**[00104]** Diluents can have varying particle sizes, and the particle size may affect the physical properties of the formulation. Microcrystalline cellulose of a certain particle size can act as a spheronization aid, to help withstand pressures during the tableting process. Microcrystalline cellulose can also help provide uniformity of particle sizes in a formulation, and larger particle sizes can improve the flowability of granules. Particle sizes of microcrystalline cellulose that may provide beneficial physical properties to formulations, including in flowability, include particles having an average diameter of about 10 µm to about 300 µm, such as about 50 µm, such as about 90 µm, and such as about 180 µm.

**[00105]** In some embodiments, the tablet includes at least one diluent that is chosen from lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, calcium phosphate, hydroxypropyl methylcellulose, sucrose, calcium sulfate, calcium lactate, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, kaolin, sodium chloride, inositol, and bentonite. In some embodiments, the tablet includes at least one diluent that is chosen from mannitol, spray-dried mannitol, lactose monohydrate, anhydrous lactose, and microcrystalline cellulose. In some embodiments, the tablet includes at least one diluent chosen from anhydrous lactose and microcrystalline cellulose. In some embodiments, the tablet includes microcrystalline cellulose. In some embodiments, the tablet includes microcrystalline cellulose selected from at least one of microcrystalline cellulose 50 µm, microcrystalline cellulose 90 µm, and microcrystalline cellulose 180 µm. In some embodiments, the tablet includes microcrystalline cellulose selected from at least one of microcrystalline cellulose 50 µm and microcrystalline cellulose 90 µm. In some embodiments, the tablet includes microcrystalline cellulose selected from at least one of microcrystalline cellulose 50 µm and

microcrystalline cellulose 180  $\mu\text{m}$ . In some embodiments, the tablet includes microcrystalline cellulose selected from at least one of microcrystalline cellulose 90  $\mu\text{m}$  and microcrystalline cellulose 180  $\mu\text{m}$ . In some embodiments, the tablet includes microcrystalline cellulose 50  $\mu\text{m}$ . In some embodiments, the tablet includes microcrystalline cellulose 90  $\mu\text{m}$ . In some embodiments, the tablet includes microcrystalline cellulose 180  $\mu\text{m}$ .

**[00106]** The total amount of diluent present in the tablet ranges from about 10 to about 50% by weight. In some embodiments, the total amount of diluent present in the tablet ranges from about 15 to about 45% by weight. In some embodiments, the total amount of diluent present in the tablet ranges from about 18 to about 40% by weight. In some embodiments, the total amount of diluent present in the tablet is about 20% by weight, about 21% by weight, about 30% by weight, about 31% by weight, about 23% by weight, or about 38% by weight.

**[00107]** In some embodiments, the tablet includes microcrystalline cellulose. In some embodiments, the amount of microcrystalline cellulose in the tablet ranges from about 15 to about 45% by weight. In some embodiments, the amount of microcrystalline cellulose in the tablet ranges from about 18 to about 40% by weight, about 20% by weight, about 21 % by weight, about 30% by weight, about 31% by weight, about 23% by weight, or about 38% by weight. In some embodiments, the amount of microcrystalline cellulose in the tablet is about 30.5% by weight. In some embodiments, the amount of microcrystalline cellulose in the tablet is about 38% by weight.

**[00108]** In some embodiments, the tablet includes about 15 to about 45% by weight, or about 18 to about 40% by weight microcrystalline cellulose selected from at least one of microcrystalline cellulose 50  $\mu\text{m}$  and microcrystalline cellulose 180  $\mu\text{m}$ . In some embodiments, the tablet includes about 15 to about 45% by weight, or about 18 to about 40% by weight microcrystalline cellulose selected from at least one of microcrystalline cellulose 50  $\mu\text{m}$ , microcrystalline cellulose 90  $\mu\text{m}$ , and microcrystalline cellulose 180  $\mu\text{m}$ . In some embodiments, the tablet includes about 30.5% by weight of microcrystalline cellulose 50  $\mu\text{m}$ . In some embodiments, the tablet includes about 30.5% by weight of microcrystalline cellulose 90  $\mu\text{m}$ . In some embodiments, the tablet includes about 20.5% by weight of microcrystalline cellulose 50  $\mu\text{m}$ . In some embodiments, the tablet includes about 20.5% by weight of microcrystalline cellulose 90  $\mu\text{m}$ . In some embodiments, the tablet includes about 10% by weight of microcrystalline cellulose 180  $\mu\text{m}$ . In some embodiments, the tablet includes about 10% by weight of microcrystalline cellulose 90  $\mu\text{m}$ .

**[00109]** In some embodiments, the tablet includes a total amount of diluent that is from about 75 mg to about 400 mg. In some embodiments, the tablet includes a total amount of

microcrystalline cellulose that is from about 75 mg to about 400 mg. In some embodiments, the tablet includes a total amount of microcrystalline cellulose that is about 128 mg, about 142 mg, about 152 mg, about 209 mg, about 234 mg, about 235 mg, or about 304 mg. In some embodiments, the tablet includes a total amount of microcrystalline cellulose 50  $\mu\text{m}$  of about 234 mg. In some embodiments, the tablet includes a total amount of microcrystalline cellulose 50  $\mu\text{m}$  of about 157 mg. In some embodiments, the tablet includes a total amount of microcrystalline cellulose 180  $\mu\text{m}$  of about 77 mg. In some embodiments, the tablet includes about 157 mg of microcrystalline cellulose 50  $\mu\text{m}$  and about 77 mg of microcrystalline cellulose 180  $\mu\text{m}$ .

**[00110]** Glidants are compounds that can lower the interparticle attraction, reduce agglomeration, and enhance the flow of powder during tablet preparation. Glidants are also referred to as flow agents, as they are used to optimize the flow properties of powder. Glidants can improve powder flowability by correcting surface irregularity, reducing interparticle friction, and decreasing surface charge.

**[00111]** In some embodiments, the tablet comprises at least one glidant. In some embodiments, the tablet optionally comprises at least one glidant. In some embodiments, the tablet does not comprise a glidant. In some embodiments, the glidant is selected from colloidal silicon dioxide and talc. In some embodiments, the glidant is colloidal silicon dioxide, which is also known as colloidal silica.

**[00112]** Colloidal silicon dioxide (also known as colloidal anhydrous silica) is available as particles with varying average specific surface areas, such as Aerosil® 200 and Aeroperl® 300 having an average specific surface area of about 200  $\text{m}^2/\text{g}$  and about 300  $\text{m}^2/\text{g}$ , respectively.

**[00113]** The total amount of glidant present in the tablet ranges from about 0 to about 5% by weight. In some embodiments, the total amount of glidant present in the tablet ranges from about 0 to about 5% by weight, such as from about 0.1 to about 2% by weight, about 0.1 to about 1.5% by weight, or about 0.1 to about 1% by weight. In some embodiments, the total amount of glidant present in the tablet is about 0.9% by weight. In some embodiments, the total amount of glidant present in the tablet is about 1.3% by weight.

**[00114]** In some embodiments, the glidant is colloidal silicon dioxide. In some embodiments, the amount of colloidal silicon dioxide present in the tablet ranges from 0 to about 5% by weight. In some embodiments, the amount of colloidal silicon dioxide present in the tablet ranges from about 0.1 to about 3% by weight, about 0.1 to about 2% by weight, about 0.1 to about 1.5% by weight, or about 0.1 to about 1% by weight. In some embodiments, the amount of colloidal silicon dioxide present in the tablet is about 0.1%, about 0.2%, about 0.3%,

about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 0.4%, or about 1.5% by weight.

**[00115]** In some embodiments, the glidant is selected from at least one of colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g, and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g. In some embodiments, the colloidal silicon dioxide is anhydrous. In some embodiments, the tablet includes colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g in a total amount of about 1.3% by weight. In some embodiments, the tablet includes colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g in a total amount of about 1.3% by weight. In some embodiments, the tablet includes colloidal silicon dioxide in a total amount that ranges between about 0.5 to about 1.5% by weight.

**[00116]** In some embodiments, the tablet includes a total amount of glidant that is from about 0 mg to about 50 mg. In some embodiments, the tablet includes a total amount of glidant that is from about 0 mg to about 20 mg. In some embodiments, the tablet includes a total amount of glidant that is from about 0 mg to about 10 mg. In some embodiments, the tablet includes a total amount of glidant that is about 3.7 mg. In some embodiments, the tablet includes a total amount of glidant that is about 8.0 mg. In some embodiments, the tablet includes a total amount of glidant that is about 9.0 mg. In some embodiments, the tablet includes a total amount of glidant that is about 10 mg.

**[00117]** Disintegrants contribute to both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid. Disintegration agents or disintegrants facilitate the disintegration of a tablet and granules and consequently affect the release of drug substance. Examples of disintegration agents include a starch, *e.g.*, a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, *e.g.*, Avicel®, Avicel® PH101, Avicel® PH 102, Avicel® PH105, Elceme® P100, Emcocel®, Vivacel®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethyl-cellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as cross linked polyvinyl N-pyrrolidone (crospovidone), a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus

pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like. In some embodiments, the at least one disintegrant is chosen from a starch, a cross-linked starch, a cellulose, a cross-linked cellulose, a cross-linked polymer, an alginate, a clay, a gum, a glycolate, bentonite, a natural sponge, a surfactant, a resin, citrus pulp, and sodium lauryl sulfate.

**[00118]** In some embodiments, the at least one disintegrant is chosen from croscarmellose sodium, croscarmellose, cross-linked sodium carboxymethyl-cellulose, cross-linked carboxymethylcellulose, cross-linked croscarmellose, crospovidone, and cross-linked polyvinylpyrrolidone. In some embodiments, the at least one disintegrant is chosen from cross linked polyvinyl N-pyrrolidone (crospovidone) and cross linked carboxymethyl cellulose (croscarmellose). In some embodiments, the at least one disintegrant comprises cross linked polyvinyl N-pyrrolidone (crospovidone) and cross linked carboxymethyl cellulose (croscarmellose). In some embodiments, the at least one disintegrant is comprises cross linked polyvinyl N-pyrrolidone (crospovidone). In some embodiments, the at least one disintegrant comprises cross linked carboxymethyl cellulose (croscarmellose). In some embodiments, the at least one disintegrant comprises croscarmellose sodium. In some embodiments, the at least one disintegrant comprises crospovidone Type A.

**[00119]** The total amount of disintegrant in the tablet ranges from about 0.1 to about 15% by weight. In some embodiments, the total amount of disintegrant in the tablet ranges from about 0.5 to about 15% by weight, about 0.1 to about 10% by weight, or about 2.0 to about 5.0% by weight. In some embodiments, the total amount of disintegrant in the tablet is about 2.0% by weight, about 3.0% by weight, about 4.0% by weight, about 5.0% by weight, about 6.0% by weight, about 7.0% by weight, about 8.0% by weight, about 9.0% by weight, or about 10% by weight. In some embodiments, the total amount of disintegrant in the tablet is about 2.0% by weight.

**[00120]** In some embodiments, the tablet includes crospovidone in about 2.0% by weight. In some embodiments, the tablet includes crospovidone in about 4.0% by weight. In some embodiments, the tablet includes crospovidone in about 10.0% by weight. In some embodiments, the tablet includes crospovidone in about 4.0% by weight and croscarmellose sodium in about 2.0% by weight.

**[00121]** In some embodiments, the tablet includes a total amount of disintegrant that is from about 1 mg to about 125 mg. In some embodiments, the tablet includes a total amount of disintegrant that is from about 10 mg to about 100 mg. In some embodiments, the tablet includes a total amount of disintegrant that is about 80 mg. In some embodiments, the tablet

includes a total amount of crospovidone that is about 80 mg. In some embodiments, the tablet includes a total amount of disintegrant that is about 15 mg. In some embodiments, the tablet includes a total amount of crospovidone that is about 15 mg. In some embodiments, the tablet includes a total amount of disintegrant that is about 14 mg. In some embodiments, the tablet includes a total amount of crospovidone that is about 14 mg. In some embodiments, the tablet includes a total amount of disintegrant that is about 8 mg. In some embodiments, the tablet includes a total amount of crospovidone that is about 8 mg. In some embodiments, the tablet includes a total amount of crospovidone that is about 25 mg and a total amount of croscarmellose sodium that is about 14 mg.

**[00122]** Lubricants are compounds that prevent, reduce, or inhibit adhesion or friction of materials. Exemplary lubricants include, *e.g.*, stearic acid, calcium hydroxide, talc, sodium stearyl fumarate, a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil, higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol (*e.g.*, PEG4000) or a methoxypolyethylene glycol such as Carbowax®, sodium oleate, sodium benzoate, glyceryl behenate, magnesium or sodium lauryl sulfate, colloidal silica such as Syloid®, Cab-O-Sil®, a starch such as corn starch, silicone oil, a surfactant, and the like. In some embodiments, the at least one lubricant is chosen from stearic acid, calcium hydroxide, talc, a hydrocarbon, a hydrogenated vegetable oil, higher fatty acids, a stearate, glycerol, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol, a methoxypolyethylene glycol, sodium oleate, sodium benzoate, glyceryl behenate, magnesium or sodium lauryl sulfate, colloidal silica, a starch, silicone oil, and a surfactant.

**[00123]** In some embodiments, the at least one lubricant is chosen from magnesium stearate and sodium stearyl fumarate. In some embodiments, the at least one lubricant is magnesium stearate. In some embodiments, the at least one lubricant is sodium stearyl fumarate. In some embodiments, the tablet does not comprise magnesium stearate. In some embodiments, the tablet does not comprise sodium stearyl fumarate.

**[00124]** In some embodiments, the total amount of lubricant in the tablet ranges from about 0.01 to about 5% by weight. In some embodiments, the total amount of lubricant in the tablet ranges from about 0.1 to about 5% by weight. In some embodiments, the total amount of lubricant in the tablet is about 1% by weight. In some embodiments, the total amount of lubricant in the tablet is about 1.25% by weight. In some embodiments, the total amount of lubricant in the tablet is about 1.2% by weight. In some embodiments, the total amount of

lubricant in the tablet is about 1.5% by weight. In some embodiments, the total amount of lubricant in the tablet is about 2.0% by weight.

**[00125]** In some embodiments, the tablet comprises magnesium stearate. In some embodiments, the amount of magnesium stearate in the tablet ranges from about 0 to about 1.5% by weight. In some embodiments, the amount of magnesium stearate in the tablet is about 1.2% by weight. In some embodiments, the amount of magnesium stearate in the tablet is about 1.25% by weight. In some embodiments, the amount of magnesium stearate in the tablet is about 1.5% by weight. In some embodiments, the amount of magnesium stearate in the tablet ranges from about 0 to about 20 mg. In some embodiments, the amount of magnesium stearate in the tablet is about 3.5 mg. In some embodiments, the amount of magnesium stearate in the tablet is about 7.2 mg. In some embodiments, the amount of magnesium stearate in the tablet is about 9.6 mg. In some embodiments, the amount of magnesium stearate in the tablet is about 11.5 mg.

**[00126]** In some embodiments, the tablet comprises sodium stearyl fumarate. In some embodiments, the amount of sodium stearyl fumarate in the tablet ranges from about 0 to about 2.0% by weight. In some embodiments, the amount of sodium stearyl fumarate in the tablet ranges from about 0 to about 20 mg. In some embodiments, the amount of sodium stearyl fumarate in the tablet is about 16 mg.

**[00127]** During preparation of the tablets of the compound of Formula (I), some of the components may be mixed separately, then later combined during processing. For example, one set of components can be blended and compacted to form dry granules. Subsequently, those intermediate dry granules can be further blended with additional components and then compressed to form tablets, which can be coated with a film-coating. The intermediate dry granules may have a certain size or shape that advantageously can provide one or more improved processing characteristics, such as, for example, a particle size that provides a flowable powder that resists aggregation. The intermediate dry granules can undergo blending with a set of additional components to form a solid material that has at least two discrete phases, with the dry granules forming an intragranular phase and the additional components forming an extragranular phase. The presence of the discrete phases can provide beneficial properties to the resultant tablet and during processing, including, for example, improved dissolution, friability, hardness properties, flowability, and tablet mass reproducibility. The granules that contain the two phases can be larger and have a more consistent particle size than granules with only one phase, which can lead to improved flow characteristics. In some embodiments, the tablet comprises an intragranular phase and an extragranular phase.

**[00128]** The intragranular phase can include the compound of Formula (I), at least one diluent, at least one disintegrant, at least one lubricant, and optionally at least one glidant.

**[00129]** In some embodiments, the at least one diluent is present in the intragranular phase in a total amount ranging from about 15% to about 45% by weight, such as about 20.5% by weight or about 30.5% by weight. In some embodiments, the at least one diluent is present in the extragranular phase in a total amount ranging from about 0% to about 15% by weight, such as about 10% by weight. In some embodiments, the at least one diluent present in the intragranular phase comprises microcrystalline cellulose 50  $\mu\text{m}$ . In some embodiments, the at least one diluent present in the intragranular phase comprises microcrystalline cellulose 90  $\mu\text{m}$ . In some embodiments, the at least one diluent present in the extragranular phase comprises microcrystalline cellulose 180  $\mu\text{m}$ . In some embodiments, the at least one diluent present in the intragranular phase comprises microcrystalline cellulose 50  $\mu\text{m}$  in a total amount of about 30.5%. In some embodiments, the at least one diluent present in the intragranular phase comprises microcrystalline cellulose 50  $\mu\text{m}$  in a total amount of about 20.5%. In some embodiments, the at least one diluent present in the intragranular phase comprises microcrystalline cellulose 90  $\mu\text{m}$  in a total amount of about 30.5%. In some embodiments, the at least one diluent present in the intragranular phase comprises microcrystalline cellulose 90  $\mu\text{m}$  in a total amount of about 20.5%. In some embodiments, the at least one diluent present in the extragranular phase comprises microcrystalline cellulose 180  $\mu\text{m}$  in a total amount of about 10%. In some embodiments, the extragranular phase does not include a diluent.

**[00130]** In some embodiments, the at least one disintegrant is present in the intragranular phase in a total amount ranging from about 1.0% to about 10% by weight, such as about 1.0% by weight, about 2.0% by weight, about 3.0% by weight, about 4.0% by weight, about 5.0% by weight, about 6.0% by weight, about 7.0% by weight, about 8.0% by weight, about 9.0% by weight, or about 10.0% by weight. In some embodiments, the at least one disintegrant is present in the intragranular phase in a total amount of about 2.0% by weight. In some embodiments, the at least one disintegrant is present in the intragranular phase in a total amount of about 4.0% by weight. In some embodiments, the at least one disintegrant is present in the intragranular phase in a total amount of about 5.0% by weight. In some embodiments, the at least one disintegrant present in the intragranular phase is chosen from cross linked polyvinyl N-pyrrolidone (crospovidone) and cross linked carboxymethyl cellulose (croscarmellose). In some embodiments, the at least one disintegrant present in the intragranular phase is crospovidone in a total amount of about 2.0% by weight. In some embodiments, the at least one disintegrant present in the intragranular phase is crospovidone in a total amount of about 5.0% by weight. In

some embodiments, the at least one disintegrant present in the intragranular phase is crospovidone in a total amount of about 3.0% by weight and croscarmellose in a total amount of about 1.0% by weight.

**[00131]** In some embodiments, the at least one disintegrant is present in the extragranular phase in a total amount ranging from about 1.0% to about 10% by weight, such as about 1.0% by weight, about 2.0% by weight, about 3.0% by weight, about 4.0% by weight, about 5.0% by weight, about 6.0% by weight, about 7.0% by weight, about 8.0% by weight, about 9.0% by weight, or about 10.0% by weight. In some embodiments, the at least one disintegrant is present in the extragranular phase in a total amount of about 2.0% by weight. In some embodiments, the at least one disintegrant is present in the extragranular phase in a total amount of about 5.0% by weight. In some embodiments, the extragranular phase does not include a disintegrant. In some embodiments, the at least one disintegrant in the extragranular phase is chosen from cross linked polyvinyl N-pyrrolidone (crospovidone) and cross linked carboxymethyl cellulose (croscarmellose). In some embodiments, the at least one disintegrant present in the intragranular phase is crospovidone in a total amount of about 2.0% by weight. In some embodiments, the at least one disintegrant present in the extragranular phase is crospovidone in a total amount of about 2.0% by weight. In some embodiments, the at least one disintegrant present in the extragranular phase is crospovidone in a total amount of about 5.0% by weight. In some embodiments, the at least one disintegrant present in the extragranular phase is crospovidone in a total amount of about 1.0% by weight and croscarmellose in a total amount of about 1.0% by weight.

**[00132]** In some embodiments, the at least one lubricant is present in the intragranular phase in a total amount ranging from about 0.01 to about 10% by weight, such as about 0.1 to about 5% by weight, such as about 0.1% by weight, about 0.2% by weight, about 0.3% by weight, about 0.4% by weight, about 0.5% by weight, about 0.6% by weight, about 0.7% by weight, about 0.8% by weight, about 0.9% by weight, or about 1.0% by weight. In some embodiments, the at least one lubricant is present in the intragranular phase in a total amount of about 0.25% by weight. In some embodiments, the at least one lubricant is present in the intragranular phase in a total amount of about 0.5% by weight. In some embodiments, the at least one lubricant is present in the intragranular phase in a total amount of about 1.0% by weight. In some embodiments, the at least one lubricant present in the intragranular phase comprises magnesium stearate or sodium stearyl fumarate. In some embodiments, the at least one lubricant present in the intragranular phase comprises magnesium stearate. In some embodiments, the at least one lubricant present in the intragranular phase comprises magnesium

stearate in a total amount of about 0.5%. In some embodiments, the at least one lubricant present in the intragranular phase comprises magnesium stearate in a total amount of about 1.0%. In some embodiments, the at least one lubricant present in the intragranular phase comprises sodium stearyl fumarate. In some embodiments, the at least one lubricant present in the intragranular phase comprises sodium stearyl fumarate in a total amount of about 1.0%.

**[00133]** In some embodiments, the at least one lubricant is present in the extragranular phase in a total amount ranging from about 0 to about 5% by weight, such as about 0.1% by weight, about 0.2% by weight, about 0.3% by weight, about 0.4% by weight, about 0.5% by weight, about 0.6% by weight, about 0.7% by weight, about 0.8% by weight, about 0.9% by weight, or about 1.0% by weight. In some embodiments, the at least one lubricant is present in the extragranular phase in a total amount of about 0.2% by weight. In some embodiments, the at least one lubricant is present in the extragranular phase in a total amount of about 0.25% by weight. In some embodiments, the at least one lubricant is present in the extragranular phase in a total amount of about 1.0% by weight. In some embodiments, the at least one lubricant present in the extragranular phase comprises magnesium stearate or sodium stearyl fumarate. In some embodiments, the at least one lubricant present in the extragranular phase comprises magnesium stearate. In some embodiments, the at least one lubricant present in the extragranular phase comprises magnesium stearate in a total amount of about 0.2%. In some embodiments, the at least one lubricant present in the extragranular phase comprises magnesium stearate in a total amount of about 1.0%. In some embodiments, the at least one lubricant present in the extragranular phase comprises sodium stearyl fumarate. In some embodiments, the at least one lubricant present in the extragranular phase comprises sodium stearyl fumarate in a total amount of about 1.0%.

**[00134]** In some embodiments, the at least one glidant is present in the intragranular phase in a total amount ranging from about 0% to about 5% by weight, such as about 0.1% by weight, about 0.2% by weight, about 0.3% by weight, about 0.4% by weight, about 0.5% by weight, about 0.6% by weight, about 0.7% by weight, about 0.8% by weight, about 0.9% by weight, about 1.0% by weight, about 1.1% by weight, about 1.2% by weight, about 1.3% by weight, about 1.4% by weight, or about 1.5% by weight. In some embodiments, the at least one glidant is present in the intragranular phase in a total amount of about 0.9% by weight. In some embodiments, the at least one glidant is present in the intragranular phase in a total amount of about 0.7% by weight.

**[00135]** In some embodiments, the at least one glidant present in the intragranular phase comprises at least one of colloidal silicon dioxide having an average specific surface area of

about 200 m<sup>2</sup>/g, and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g. In some embodiments, the at least one glidant present in the intragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g in a total amount of about 0.9% by weight. In some embodiments, the at least one glidant present in the intragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g in a total amount of about 0.7% by weight. In some embodiments, the at least one glidant present in the intragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g in a total amount of about 0.9% by weight. In some embodiments, the at least one glidant present in the intragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g in a total amount of about 0.7% by weight.

**[00136]** In some embodiments, the at least one glidant is present in the extragranular phase in a total amount ranging from about 0% to about 5% by weight, such as about 0.1% by weight, about 0.2% by weight, about 0.3% by weight, about 0.4% by weight, about 0.5% by weight, about 0.6% by weight, about 0.7% by weight, about 0.8% by weight, about 0.9% by weight, about 1.0% by weight, about 1.1% by weight, about 1.2% by weight, about 1.3% by weight, about 1.4% by weight, or about 1.5% by weight. In some embodiments, the at least one glidant is present in the extragranular phase in a total amount of about 0.4% by weight. In some embodiments, the at least one glidant is present in the extragranular phase in a total amount of about 0.6% by weight.

**[00137]** In some embodiments, the at least one glidant present in the extragranular phase comprises at least one of colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g, and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g. In some embodiments, the at least one glidant present in the extragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g in a total amount of about 0.4% by weight. In some embodiments, the at least one glidant present in the extragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g in a total amount of about 0.6% by weight. In some embodiments, the at least one glidant present in the extragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g in a total amount of about 0.4% by weight. In some embodiments, the at least one glidant present in the extragranular phase comprises colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g in a total amount of about 0.6% by weight.

**[00138]** In some embodiments, the tablet includes at least one compound chosen from the

compound of Formula (I) and pharmaceutically acceptable salts thereof, at least one diluent present in an amount ranging from about 10% to about 50% by weight, at least one disintegrant present in an amount ranging from about 0.1% to about 15% by weight, at least one lubricant present in an amount ranging from about 0.01% to about 5% by weight, and optionally, at least one glidant. In embodiments wherein the at least one glidant is present, the glidant is present in an amount greater than 0% by weight to about 5% by weight, such as in an amount ranging from about 0.01% to about 5% by weight.

**[00139]** In some embodiments, the intragranular phase includes the compound of Formula (I), microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. In some embodiments, the extragranular phase includes magnesium stearate. In some embodiments, the intragranular phase includes the compound of Formula (I), microcrystalline cellulose, crospovidone, and sodium stearyl fumarate. In some embodiments, the extragranular phase includes sodium stearyl fumarate. In some embodiments, the intragranular phase includes the compound of Formula (I), microcrystalline cellulose, at least one of crospovidone and croscarmellose, magnesium stearate, and colloidal silicon dioxide. In some embodiments, the extragranular phase includes microcrystalline cellulose, at least one of crospovidone and croscarmellose, magnesium stearate, and colloidal silicon dioxide.

**[00140]** In some embodiments, the intragranular phase includes the compound of Formula (I), microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. In some embodiments, the extragranular phase includes magnesium stearate and colloidal silicon dioxide.

**[00141]** Binders impart cohesive qualities and include, *e.g.*, alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (*e.g.*, Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (*e.g.*, Klucel®), ethylcellulose (*e.g.*, Ethocel®), and microcrystalline cellulose (*e.g.*, Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinyl-pyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (*e.g.*, Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (*e.g.*, Xylitab®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum mucilage of isapol husks, polyvinylpyrrolidone (*e.g.*, Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, polyethylene oxide, waxes, sodium alginate, and the like.

**[00142]** Those skilled in the art will appreciate that the selection of excipients may depend upon the process used to make the tablets before compression, whether that process

involves blending or dry granulation. For example, dry granulation may involve compacting to form dry granules and then adding excipients later, including a binder. Of course, modifications of this may occur, such as adding materials later, as will be appreciated by skilled persons.

**[00143]** In some embodiments, the at least one binder is chosen from alginic acid, carboxymethylcellulose, methylcellulose (*e.g.*, Methocel®), hydroxypropyl methylcellulose (Hypromellose, HPMC), hydroxyethylcellulose, hydroxypropylcellulose (*e.g.*, Klucel®), ethylcellulose (*e.g.*, Ethocel®), microcrystalline cellulose (*e.g.*, Avicel®), microcrystalline dextrose, amylose, magnesium aluminum silicate, gelatin, polyvinyl-pyrrolidone/vinyl acetate copolymer; crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, sucrose (*e.g.*, Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (*e.g.*, Xylitab®), lactose; acacia, tragacanth, ghatti gum mucilage of isapol husks, and polyvinylpyrrolidone (*e.g.*, Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10). In an embodiment, the binder comprises hydroxypropylcellulose.

**[00144] Processes Of Preparing The Formulations**

**[00145]** Pharmaceutical preparations disclosed herein can be obtained by mixing at least one solid excipient described herein, with a solid form of the compound of Formula (I) described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable excipients, if desired, to obtain tablets.

**[00146]** Additional steps include one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) fusion, or (6) extrusion. See, *e.g.*, Lachman et al., *The Theory and Practice of Industrial Pharmacy*, 3rd ed. (1986). Other methods include, *e.g.*, spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (*e.g.*, wurster coating), tangential coating, top spraying, tableting, extruding, extrusion/spheronization, and the like.

**[00147]** In some embodiments, the preparation of the tablets disclosed herein include weighing, sieving, mixing, compaction, tableting, and film-coating steps.

**[00148]** In some embodiments, the tablets prepared using the formulations disclosed herein are compacted at a pressure ranging from about 30 to about 60 bars, such as of about 36 bars. In some embodiments, the tablets prepared using the formulations disclosed herein have a mean resistance to crushing of  $250\text{N} \pm 50\text{N}$ . In some embodiments, the tablets prepared using the formulations disclosed herein have a friability  $< 1\%$  after 4 minutes and 30 minutes. In some embodiments, the tablets prepared using the formulations disclosed herein have a disintegration time  $< 15$  minutes. In some embodiments, the tablets prepared using the

formulations disclosed herein have at least one of the following characteristics: a mean resistance to crushing of  $250\text{N} \pm 50\text{N}$ , a friability  $< 1\%$  after 4 minutes and 30 minutes, and a disintegration time  $< 15$  minutes.

**[00149]** In some embodiments, the tablet includes at least one coating layer. In some embodiments, the coating layer is a film-coating layer. The coating layer can include hydroxypropyl methylcellulose, also referred to as hypromellose. In some embodiments, the coating layer comprises at least one of titanium dioxide and polyethylene glycol. In some embodiments, the coating layer comprises titanium dioxide and polyethylene glycol. In some embodiments, the coating layer comprises hydroxypropyl methylcellulose. In some embodiments, the coating layer can mask or improve the taste of the tablet, and can include a taste masking agent.

**[00150]** In some embodiments, the coating layer comprises about 1% to about 8 % by weight of the tablet. In some embodiments, the coating layer comprises about 1% by weight, about 2 % by weight, about 3 % by weight, about 4 % by weight, about 5 % by weight, about 6 % by weight, about 7 % by weight, or about 8 % by weight of the tablet.

**[00151]** In some embodiments, the coating layer includes 36% lactose monohydrate, 28% hypromellose (15 mPa.s), 26% titanium dioxide (E171) and 10% macrogol 3000-polyethylene glycol 3000 in an amount of about 2 to 4 % by weight of the tablet. In some embodiments, the coating layer includes lactose monohydrate, hypromellose, titanium dioxide and macrogol 3000-polyethylene glycol 3000 in an amount of about 3 % by weight of the tablet.

**[00152]** In some embodiments, the coating layer includes 40% of polyvinyl alcohol hydrolyzed, 20.2% of macrogol/PEG, 21.5% of titanium dioxide, 14.8% of talc and 3.5% of FD&C yellow #6 (Sunset Yellow FCF Aluminum Lake, USFDA Pigment Certification AZ7623, Regulation (EC) No 1333/2008). In some embodiments, the coating layer includes polyvinyl alcohol hydrolyzed, macrogol/PEG, titanium dioxide, talc and a pigment in an amount of about 3 % by weight of the tablet.

**[00153]** In some embodiments, the pharmaceutical formulation is free of titanium dioxide.

**[00154]** Colorants, surfactants, anti-adhesion agents, antifoaming agents, lubricants (*e.g.*, carnauba wax or PEG) and other additives may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product. In some embodiments, the coating layer is white. In some embodiments, the coating layer is orange.

**[00155]** In some embodiments, the tablets are packaged in a blister pack. The blister packs can be made from any appropriate material. Examples include polyvinyl-

polychlorotrifluoroethylene in the forming film and hardened aluminum foil as lidding.

[00156] In some embodiments, the tablets are packaged in a bottle. The bottle can be made from any appropriate material.

**[00157] Therapeutic Methods**

[00158] Provided herein are methods of treating a disease or condition mediated by BTK comprising administering to a subject in need thereof a formulation comprising a therapeutically effective amount of the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. In some embodiments the therapeutically effective amount is about 50 mg to about 900 mg. In some embodiments the therapeutically effective amount is about 200 mg. In some embodiments the therapeutically effective amount is about 300 mg. In some embodiments the therapeutically effective amount is about 400 mg. In some embodiments the therapeutically effective amount is about 500 mg. In some embodiments the therapeutically effective amount is about 600 mg. In some embodiments the therapeutically effective amount is about 800 mg. In some embodiments, the subject is a mammal. In some embodiments, the mammal is a human.

[00159] Also provided herein are uses of the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for the manufacture of a medicament to treat a disease or condition mediated by BTK. In some embodiments, the use of the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for the manufacture of a medicament to treat a disease or condition mediated by BTK, comprises use of a therapeutically effective amount of the compound of Formula (I). In some embodiments, the therapeutically effective amount of the compound of Formula (I) is about 50 mg to about 900 mg. In some embodiments the therapeutically effective amount is about 200 mg. In some embodiments the therapeutically effective amount is about 300 mg. In some embodiments the therapeutically effective amount is about 400 mg. In some embodiments the therapeutically effective amount is about 500 mg. In some embodiments the therapeutically effective amount is about 600 mg. In some embodiments the therapeutically

effective amount is about 800 mg. In some embodiments, the medicament is for use in treating a mammal. In some embodiments, the mammal is a human.

**[00160]** Further provided herein are uses of the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for the treatment of a disease or condition mediated by BTK. In some embodiments, the use of the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for the treatment of a disease or condition mediated by BTK, comprises use of a the therapeutically effective amount of the compound of Formula (I). In some embodiments, the therapeutically effective amount of the compound of Formula (I) is about 50 mg to about 900 mg. In some embodiments the therapeutically effective amount is about 200 mg. In some embodiments the therapeutically effective amount is about 300 mg. In some embodiments the therapeutically effective amount is about 400 mg. In some embodiments the therapeutically effective amount is about 500 mg. In some embodiments the therapeutically effective amount is about 600 mg. In some embodiments the therapeutically effective amount is about 800 mg. In some embodiments, the use is for the treatment of a mammal. In some embodiments, the mammal is a human.

**[00161]** Additionally provided herein is the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in the treatment of a disease or condition mediated by BTK. Also provided herein is the compound of Formula (I), 2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, for use in the manufacture of medicament for the treatment of a disease or condition mediated by BTK.

**[00162]** In some embodiments, a dose of about 50-100 mg, 100-150 mg, 150-200 mg, 200-250 mg, 250-300 mg, 300-350 mg, 350-400 mg, 400-450 mg, 450-500 mg, 500-550 mg, 550-600 mg, 600-650 mg, 650-700 mg, 700-750 mg, 750-800 mg, 800-850 mg, or 850-900 mg is administered. In some embodiments, the dose is about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg. In some embodiments, the dose is about 200 mg. In some embodiments, the dose is about 300 mg.

In some embodiments, the dose is about 400 mg. In some embodiments the dose is about 500 mg. In some embodiments, the dose is about 600 mg. In some embodiments, the dose is about 800 mg. In some embodiments, the dose is about 900 mg.

**[00163]** In some embodiments, the dose is administered daily. The daily dose can be delivered as a single dose or split into multiple parts. For example, in some embodiments, the dose is administered once a day (*e.g.*, about every 24 hours). In some embodiments, the dose is administered twice daily. In some embodiments, the dose is subdivided in two parts to be administered twice per day (*e.g.*, about every 12 hours). In some embodiments, the dose is subdivided in three parts to be administered three times per day (*e.g.*, about every 8 hours). In some embodiments, the dose is subdivided in four parts to be administered four times per day (*e.g.*, about every 6 hours).

**[00164]** In some embodiments, the dose is administered orally. In some embodiments, the dose is administered in a form of tablets. In some embodiments, the dose is administered in the form of pills, capsules, semisolids, powders, sustained release formulations, or any other appropriate compositions.

**[00165]** In some embodiments, the subject is administered the BTK inhibitor compound of Formula (I) for a period of about 4, 8, 12, 16, 20, 24, or 26 weeks. In some embodiments, the subject is administered the BTK inhibitor compound of Formula (I) for a period of about 6, 12, 18, 24, 30, 36, 42, or 48 months. In some embodiments, the dose is once daily. In some embodiments, the dose is twice daily.

**[00166]** In some embodiments, the BTK inhibitor compound of Formula (I) is administered as monotherapy. In some embodiments, the method comprises administering the BTK inhibitor compound of Formula (I) and at least one additional therapeutic agent. The additional therapeutic agent may be administered concurrently or sequentially with the compound of Formula (I).

**[00167]** Determination of the frequency of administration can be made by persons skilled in the art, such as an attending physician based on considerations of the condition being treated, age of the subject being treated, severity of the condition being treated, general state of health of the subject being treated and the like.

**[00168]** In some embodiments, the compound of Formula (I) is administered in a therapeutically effective amount for treatment of various conditions or diseases, such as, *e.g.*, at least one of acne, allergy, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson syndrome, toxic epidermal necrolysis (TEN), pemphigus vulgaris, pemphigus foliaceus, ankylosing spondylitis,

antiphospholipid antibody syndrome, vasculitis, Guillain-Barre syndrome, scleroderma, Wegener's granulomatosis, psoriasis, granulomatosis with polyangiitis, thrombotic thrombocytopenic purpura, polyarteritis nodosa, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, asthma, moderate-to-severe asthma, mild asthma, moderate asthma, severe asthma, asthma that is not well controlled, autoimmune hepatitis, Behcet's disease, Grave's disease, nephritis, pancreatitis, primary biliary cirrhosis, ulcerative colitis, colitis, conjunctivitis, dermatitis, atopic dermatitis, drug eruptions, drug-induced thrombocytopenia (DITP), vaccine-induced thrombosis and thrombocytopenia (VITT), eczema, folliculitis decalvans, pseudofolliculitis barbae, leukoclastic vasculitis, hidradenitis suppurativa, palmar plantar pustulosis, Lichenoid dermatitis, mycosis fungoides, sweet syndrome, follicular lymphoma, diffuse large B cell lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom 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, non-Hodgkin lymphoma, warm autoimmune hemolytic anemia (wAIHA), B-cell acute lymphoblastic leukemia (B-ALL), small lymphocytic lymphoma (SLL), intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, B-cell non-Hodgkin lymphoma, idiopathic thrombocytopenic purpura, IgG4-related diseases (IgG4-RD) and flares thereof, antiphospholipid syndrome (APS), membranous nephropathy (MN), immune thrombocytopenia, inflammatory bowel disease, itch associated with atopic dermatitis, lupus, cutaneous lupus, cutaneous lupus erythematosus, lupus nephritis, mixed connective tissue disease, multiple myeloma, multiple sclerosis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), sepsis, sepsis induced acute lung injury, diffuse alveolar damage (DAD), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (sHLH), cytokine release syndrome (CRS), cutaneous form of systemic sclerosis (CREST), cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, urticaria, chronic spontaneous urticaria (CSU), chronic idiopathic urticaria (CIU), AI urticaria, and IgA nephropathy.

**[00169]** The therapeutically effective amount is typically dependent on the weight of the subject being treated, his or her physical or health condition, the extensiveness of the condition to be treated, or the age of the subject being treated, pharmaceutical formulation methods, and/or administration methods (*e.g.*, administration time and administration route).

**[00170]** In some embodiments, the dose is administered with food. In some

embodiments, the dose is administered once daily with food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered with food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered once daily with food. In some embodiments, the dose of 400 mg is administered once daily with food. In some embodiments, the dose of 600 mg is administered once daily with food. In some embodiments, the dose is administered in tablets. In some embodiments, the dose is administered in tablets with food. In some embodiments, the dose is administered once daily in tablets. In some embodiments, the dose is administered once daily in tablets with food. In some embodiments, the dose of 400 mg is administered in tablets. In some embodiments, the dose of 400 mg is administered in tablets with food. In some embodiments, the dose of 400 mg is administered once daily in tablets. In some embodiments, the dose of 400 mg is administered once daily in tablets with food. In some embodiments, the dose of 600 mg is administered in tablets. In some embodiments, the dose of 600 mg is administered in tablets with food. In some embodiments, the dose of 600 mg is administered once daily in tablets. In some embodiments, the dose of 600 mg is administered once daily in tablets with food.

**[00171]** In some embodiments, the dose is administered twice daily with food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered with food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered twice daily with food. In some embodiments, the dose of 400 mg is administered twice daily with food. In some embodiments, the dose of 600 mg is administered twice daily with food. In some embodiments, the dose is administered in tablets. In some embodiments, the dose is administered in tablets with food. In some embodiments, the dose is administered twice daily in tablets. In some embodiments, the dose is administered twice daily in tablets with food. In some embodiments, the dose of 400 mg is administered twice daily in tablets. In some embodiments, the dose of 400 mg is administered twice daily in tablets with food. In some embodiments, the dose of 600 mg is administered twice daily in tablets. In some embodiments, the dose of 600 mg is administered twice daily in tablets with food.

**[00172]** In some embodiments, the dose is administered without food. In some embodiments, the dose is administered once daily without food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered without food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered once daily without food. In some embodiments, the dose of 400 mg is administered once daily without food. In some embodiments, the dose of 600 mg is administered once daily without food. In some embodiments, the dose is administered in tablets without food. In some

embodiments, the dose is administered once daily in tablets without food. In some embodiments, the dose of 400 mg is administered in tablets without food. In some embodiments, the dose of 400 mg is administered once daily in tablets without food. In some embodiments, the dose of 600 mg is administered in tablets without food. In some embodiments, the dose of 600 mg is administered once daily in tablets without food.

[00173] In some embodiments, the dose is administered twice daily without food. In some embodiments, the dose of 200 mg, 300 mg, 400 mg, 600 mg, or 800 mg is administered twice daily without food. In some embodiments, the dose of 400 mg is administered twice daily without food. In some embodiments, the dose of 600 mg is administered twice daily without food. In some embodiments, the dose is administered twice daily in tablets without food. In some embodiments, the dose of 400 mg is administered twice daily in tablets without food. In some embodiments, the dose of 600 mg is administered twice daily in tablets without food.

[00174] In some embodiments, the dose is 400 mg administered once daily. In some embodiments, the dose is 600 mg administered once daily.

[00175] In some embodiments, the dose is 400 mg administered twice daily. In some embodiments, the dose is 600 mg administered twice daily.

[00176] The foregoing disclosure has been described in some detail by way of illustration and example, for purposes of clarity and understanding. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the disclosure should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

## EXAMPLES

[00177] The following Examples are presented by way of illustration, not limitation. One skilled in the art can modify the procedures set forth in the illustrative examples to arrive at the desired products.

[00178] In accordance with the current disclosure, formulations including the compound of Formula (I) can be prepared as described herein.

[00179] **Example 1: Immediate Release Tablet Formulation (400 mg, amorphous)**

[00180] A film-coated tablet containing 400 mg of amorphous rilzabrutinib was prepared, with the components listed in Table 3, below. A homothetical formulation of the tablets will be prepared containing 300 mg of amorphous rilzabrutinib, for use in Example 7.

Table 3. Composition of amorphous rilzabrutinib 400 mg tablet, film-coated

| Component                                                               | Unit<br>weight<br>(mg/tablet) | % (w/w)       |               | Function                     |
|-------------------------------------------------------------------------|-------------------------------|---------------|---------------|------------------------------|
|                                                                         |                               | Intragranular | Extragranular |                              |
| Rilzabrutinib drug<br>substance                                         | 400.00                        | 50.0          | -             | Drug<br>Substance            |
| Microcrystalline<br>cellulose PH101 <sup>a</sup>                        | 304.00                        | 38.0          | -             | Diluent                      |
| Crospovidone,<br>Type A                                                 | 80.00                         | 5.0           | 5.0           | Disintegrant                 |
| Sodium stearyl<br>fumarate                                              | 16.00                         | 1.0           | 1.0           | Lubricant                    |
| <i>Total weight of<br/>core tablet</i>                                  | 800.00                        | 100           |               |                              |
| Film coating                                                            |                               |               |               |                              |
| Ready-to-use<br>orange or white<br>film-coating<br>agent <sup>b,c</sup> | 24.0                          | 3.0           |               | Film-<br>coating<br>Material |
| <i>Total weight of<br/>film-coated tablet</i>                           | 824.00 g                      |               |               |                              |

- a The microcrystalline cellulose amount is adjusted to compensate for rilzabrutinib drug substance weight.
- b Purified water from the spray coating suspension is removed by drying during the process.
- c Represents 3% weight gain on the tablet core weight. Opadry II 85F130006 or Opadry II 85F18422 white may be used.

**[00181] Microcrystalline cellulose.** Microcrystalline cellulose (MCC) was used as a diluent for direct compression and roller compaction. Microcrystalline cellulose is used in approved tablet drug products, primarily as a diluent in oral tablet formulations. In addition to

its use as a diluent, microcrystalline cellulose also has good compressibility properties that make it useful in tableting. In rilzabrutinib tablet manufacturing, MCC is added to the formulation to provide good compaction/compressibility and adhesion.

[00182] The MCC used in the rilzabrutinib tablets described herein is Avicel PH101.

[00183] **Crospovidone.** Crospovidone is a water-insoluble cross-linked polyvinyl N-pyrrolidone. It is a nonionic disintegrant and dissolution enhancement agent that can be used in tablets prepared by direct-compression and dry-granulation methods. It is considered a super disintegrant as it rapidly exhibits high capillary activity and pronounced hydration capacity. In the formulation described herein, the rilzabrutinib is designed as an immediate-release tablet so that rapid disintegration can occur to ensure maximum bioavailability.

[00184] The particle size of crospovidone affects the disintegration process, and larger particles can provide a faster disintegration. As size increases, the intra-particle porosity increases, leading to larger water uptake and faster disintegration. Disintegrants can be more effective if used both intra- and extra-granularly. In general, disintegrants added only intra-granularly are not as effective as disintegrants added extra-granularly. For rilzabrutinib tablets, crospovidone is used at a 5% level intra-granularly and another 5% is added extra-granularly. This ensures that the tablet disintegrates quickly and improves dissolution.

[00185] The crospovidone grade selected for this product is Type A grade, a multi-compendial grade crospovidone which has a large particle size, swell pressure and fast disintegration time.

[00186] **Sodium stearyl fumarate.** Sodium stearyl fumarate (SSF) is a tablet lubricant designed for formulations in which a high-speed direct compression of tablets is desired. SSF can be used to minimize sticking of the blend to the rollers and facilitate tablet ejection during compression. Using SSF can be beneficial as compared to other lubricants, *e.g.*, magnesium stearate, including a high degree of drug compatibility and robustness to over-lubrication. In addition, SSF can be preferred over magnesium stearate because it can enhance faster dissolution rates, harder tablets, and protect from over-blending.

[00187] SSF used in rilzabrutinib tablets is a multi-compendial grade SSF, manufactured by JRS Pharma.

[00188] **Film Coating Agent.** Ready-to-use orange film-coating agent, Opadry II 85F130006, was manufactured by Colorcon and is composed of a mixture containing polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and aluminum lake pigments FD&C yellow #6.

[00189] In the tablet formulation described herein, the coating agent is dispersed in

purified water and then sprayed on the tablet cores to form a water-soluble film-coat, which is a cosmetic coating and can allow immediate disintegration of the tablets for fast release of rilzabrutinib.

[00190] Tablets containing 400 mg of amorphous rilzabrutinib had a total mass of the core tablet of 800 mg per tablet (not including film coating). This is shown in Table 4, below.

Table 4. Composition of amorphous rilzabrutinib formulation (400 mg)

| Component                                           | Unit<br>weight<br>(mg/tablet) | % (w/w)          |               | Function               |
|-----------------------------------------------------|-------------------------------|------------------|---------------|------------------------|
|                                                     |                               | Intragranular    | Extragranular |                        |
| Rilzabrutinib drug substance                        | 400.0                         | 50.0             | -             | Drug Substance         |
| Microcrystalline cellulose                          | 304.0                         | 38.0             | -             | Diluent                |
| Crospovidone, Type A                                | 80.0                          | 5.0              | 5.0           | Disintegrant           |
| Sodium stearyl fumarate                             | 16.0                          | 1.0              | 1.0           | Lubricant              |
| <i>Total mass of core tablet</i>                    | 800.0                         | 100              |               |                        |
| Film coating                                        |                               |                  |               |                        |
| Ready-to-use orange film-coating agent <sup>c</sup> | 24.0 <sup>b</sup>             | 3.0 <sup>b</sup> |               | Film-coating component |
| Purified water <sup>a</sup>                         | -                             | q.s.             |               | Film-coating solvent   |
| <i>Total mass of film-coated tablet</i>             | 824.0                         |                  |               |                        |

a Purified water from the spray coating suspension is removed by drying during the

- process.
- b Theoretical quantity indicated, corresponding to a targeted weight gain of 3% on the core tablet weight. Spraying is stopped once the weight gain reaches approximately 3%.
- c Ready to use orange film coating; Opadry II® complete film coating system 85F130006 may be used.

[00191]        **Example 2: Crystalline Formulation (270 mg)**

[00192]        A tablet containing 270 mg of crystalline Form B of rilzabrutinib was prepared, with the components listed in Table 5, below.

Table 5. Rilzabrutinib 270 mg tablet (crystalline)

| Intragranular components        |                |                     |
|---------------------------------|----------------|---------------------|
| Rilzabrutinib, crystalline      | drug substance | 65.00 wt % (270 mg) |
| Microcrystalline cellulose 50µm | diluent        | 30.85 wt %          |
| Crospovidone Type A             | disintegrant   | 2.00 wt %           |
| Magnesium Stearate              | lubricant      | 0.25 wt %           |
| Colloidal silicon dioxide       | glidant        | 0.90 wt %           |
| Extragranular components        |                |                     |
| Magnesium Stearate              | lubricant      | 1.00 wt. %          |

- [00193]        The final tablet mass was 416 mg ± 3% (404 – 428 mg).
- [00194]        The process for preparing the tablets described herein included weighing, sieving, mixing, compaction, tableting, and film-coating steps.

[00195]        **Example 3: Crystalline Formulations (400 mg, 450 mg)**

[00196]        Two formulations for tablets containing crystalline Form B rilzabrutinib, one with 400 mg of drug substance and one with 450 mg of drug substance, were prepared. The components for these two formulations are listed in Table 6, below. Numbers in the table represent the percentage of each component by weight, relative to the total tablet weight.

Table 6. Composition of rilzabrutinib formulations

| Component | Function | Crystalline<br>(400 mg) | Crystalline<br>(450 mg) |
|-----------|----------|-------------------------|-------------------------|
|-----------|----------|-------------------------|-------------------------|

|                                     |                |              |              |
|-------------------------------------|----------------|--------------|--------------|
| <b>Intragranular</b>                |                |              |              |
| Rilzabrutinib crystalline           | Drug Substance | 65.0         | 65.0         |
| Microcrystalline Cellulose 50µm     | Diluent        | 23.0         | 30.2         |
| Hydroxypropylcellulose              | Binder         | 2.0          | -            |
| Crospovidone type A                 | Disintegrant   | 3.0          | 2.0          |
| Croscarmellose sodium               | Disintegrant   | 1.0          | -            |
| Colloidal anhydrous silicon dioxide | Glidant        | 0.9          | 0.9          |
| Sodium stearyl fumarate             | Lubricant      | -            | -            |
| Magnesium stearate                  | Lubricant      | 1.0          | 0.5          |
| <b>Extragranular</b>                |                |              |              |
| Microcrystalline Cellulose 50µm     | Diluent        | 1.5          | -            |
| Colloidal anhydrous silicon dioxide | Glidant        | 0.4          | 0.4          |
| Crospovidone Type A                 | Disintegrant   | 1.0          | -            |
| Croscarmellose                      | Disintegrant   | 1.0          | -            |
| Magnesium stearate                  | Lubricant      | 0.20         | 1.0          |
| Sodium stearyl fumarate             | Lubricant      | -            | -            |
| <b>TOTAL</b>                        |                | <b>100.0</b> | <b>100.0</b> |
| Orange film-coating agent           | Coating agent  | 3.0          | -            |
| White film-coating agent*           | Coating agent  | -            | 4.0          |

\* TiO<sub>2</sub>-free

[00197] In this study, it was determined that hydroxypropylcellulose could be removed from the formulation without adversely affecting the physical characteristics of the tablet. Additionally, it was determined that one disintegrant was sufficient, that magnesium stearate and silicon dioxide are sufficient for the extragranular phase, that use of magnesium stearate in the extragranular phase can reduce sticking of the material during processing, and that a TiO<sub>2</sub>-free

white film-coating agent can be used.

**[00198] Example 4: Additional Crystalline Formulations (500 mg)**

**[00199]** A formulation for tablets containing 500 mg of crystalline Form B rilzabrutinib was prepared. The components for this formulation are listed in Table 7, below.

Table 7. Composition of 500 mg crystalline rilzabrutinib formulation

| Component                              | Centesimal composition [%] | Composition per unit [mg/unit] |
|----------------------------------------|----------------------------|--------------------------------|
| <b>Intragranular</b>                   |                            |                                |
| RILZABRUTINIB<br>CRYSTALLINE           | 65.00                      | 500.00                         |
| Microcrystalline Cellulose<br>50 µm    | 30.45                      | 234.23                         |
| Colloidal anhydrous silicon<br>dioxide | 0.90                       | 6.92                           |
| Crospovidone Type A                    | 2.00                       | 15.38                          |
| Magnesium Stearate                     | 0.25                       | 1.92                           |
| <b>Extragranular</b>                   |                            |                                |
| Magnesium Stearate                     | 1.00                       | 7.69                           |
| Colloidal anhydrous silicon<br>dioxide | 0.40                       | 3.08                           |
| <b>Core tablet terminated at</b>       | <b>100.00 %</b>            | <b>769.23 mg</b>               |
| <b>Film-coating</b>                    |                            |                                |
| Opadry® 32F38977 white <sup>a</sup>    | 3.0                        | 23.08                          |
| Purified water <sup>b</sup>            | Sufficient<br>quantity     |                                |
| <b>Film-coated terminated at</b>       |                            | <b>792.31 mg</b>               |

a Opadry® II 32F38977 is composed of 36% lactose monohydrate, 28% hypromellose (15 mPa.s, 26% titanium dioxide (E171), and 10% macrogol 3000-polyethylene glycol 3000.

b Purified water from the spray coating suspension is removed by drying during the process.

[00200] **Example 5: An Additional 500 mg Crystalline Exemplary Formulation**

[00201] An additional formulation for tablets containing 500 mg of crystalline Form B rilzabrutinib was prepared. The components for this formulation are listed in Table 8, below.

Table 8. A Crystalline Formulation for 500 mg Rilzabrutinib

| Component                           | Function       | Weight % for crystalline formulation (500 mg) |
|-------------------------------------|----------------|-----------------------------------------------|
| <b>Intragranular</b>                |                |                                               |
| Rilzabrutinib, crystalline          | Drug Substance | 65.0                                          |
| Microcrystalline Cellulose          | Diluent        | 30.45                                         |
| Crospovidone type A                 | Disintegrant   | 2.0                                           |
| Colloidal anhydrous silicon dioxide | Glidant        | 0.9                                           |
| Magnesium stearate                  | Lubricant      | 0.25                                          |
| <b>Extragranular</b>                |                |                                               |
| Microcrystalline Cellulose          | Diluent        | -                                             |
| Colloidal anhydrous silicon dioxide | Glidant        | 0.4                                           |
| Magnesium stearate                  | Lubricant      | 1.0                                           |
| <b>TOTAL</b>                        |                | <b>100.0</b>                                  |
| White film-coating agent            | Coating agent  | 3.0                                           |

[00202] Tablets were made with the formulation shown in Table 8. An additional batch was made with 0.50 weight % of magnesium stearate in the intragranular phase. Tablet mass was  $769.23 \pm 3\%$ .

[00203] It was determined that using a white coating with titanium dioxide was beneficial to have a suitable color for the tablets. There were issues with flowing of the material during processing at the compression step.

[00204] **Example 6: Colloidal Silicon Dioxide/MCC variations (400 mg crystalline)**

[00205] Six additional formulations for tablets containing 400 mg of crystalline Form B rilzabrutinib will be prepared, to evaluate the effects of varying the types of colloidal silicon

dioxide and microcrystalline cellulose (MCC) used in the tablets. The components for these formulations are listed in Table 9, below.

Table 9. Additional Formulations for 400 mg Crystalline Rilzabrutinib Tablets

| <b>Formula w/w %</b>              | <b>1</b>      | <b>2</b>      | <b>3</b>      | <b>4</b>      | <b>5</b>      | <b>6</b>      |
|-----------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| <b>Intragranular</b>              |               |               |               |               |               |               |
| Rilzabrutinib, crystalline        | 65.00         | 65.00         | 65.00         | 65.00         | 65.00         | 65.00         |
| Microcrystalline cellulose 50 µm  | 30.45         | 30.45         | 30.45         | 20.45         | 20.45         | 20.45         |
| Crospovidone Type A               | 2.00          | 2.00          | 2.00          | 2.00          | 2.00          | 2.00          |
| colloidal silica Aerosil 200      | 0.9           | -             | 0.7           | 0.7           | 0.9           | -             |
| colloidal silica Aeroperl 300     | -             | 0.9           | -             | -             | -             | 0.9           |
| Magnesium stearate                | 0.25          | 0.25          | 0.25          | 0.25          | 0.25          | 0.25          |
| <b>Extragranular</b>              |               |               |               |               |               |               |
| colloidal silica Aerosil 200      | 0.4           | -             | 0.6           | 0.6           | 0.4           | -             |
| colloidal silica Aeroperl 300     | -             | 0.4           | -             | -             | -             | 0.4           |
| Microcrystalline cellulose 180 µm | -             | -             | -             | 10.0          | 10.0          | 10.0          |
| Magnesium stearate                | 1.00          | 1.00          | 1.00          | 1.00          | 1.00          | 1.00          |
| <b>TOTAL</b>                      | <b>100.00</b> | <b>100.00</b> | <b>100.00</b> | <b>100.00</b> | <b>100.00</b> | <b>100.00</b> |

[00206] These formulations for tablets containing 400 mg of crystalline rilzabrutinib will determine an optimum formulation for future use.

**[00207] Example 7: Food effect and relative bioavailability study of rilzabrutinib in healthy participants.**

**[00208]** A randomized, open-label, single-dose, 4-period, 4-sequence, crossover Phase I relative bioavailability study comparing crystalline formulation tablet versus reference amorphous formulation tablet of rilzabrutinib in fasted and fed conditions in healthy male and female participants was performed. IMP = investigational medicinal product.

**[00209]** The amorphous formulation was studied with a dose of two 300 mg amorphous tablets (for a total dose of 600 mg rilzabrutinib; IMP1) and the crystalline formulation was studied with a dose of one 500 mg crystalline tablet (IMP2).

**[00210]** This study was performed with healthy volunteers.

**[00211]** Summary of study design. This was a randomized, open-label, single dose, 4-period, 4-sequence, crossover Phase I relative bioavailability study comparing crystalline formulation tablet to reference amorphous formulation tablet of rilzabrutinib in fasted and fed (high fat meal) conditions in healthy male and female participants aged 18 to 55 years.

**[00212]** The total study duration per participant was approximately 36 days, including:

**[00213]** Screening: 28 days (Day -28 to Day -1).

**[00214]** Treatment periods: once successfully screened, enrolled participants will be randomized to 1 of 4 treatment sequences with 4 single dose treatment periods. Duration of each period of the study for 1 participant: 1 day of treatment followed by 1 day washout.

**[00215]** Washout: One day washout is planned after each treatment period hence providing 2 days between doses.

**[00216]** Safety follow-up: participants were asked to participate in an end-of-study safety assessment upon discharge from the clinical study unit, i.e., on Day 8 of the study, 1 day after last IMP administration on Day 1 of the fourth treatment period.

**[00217]** Primary Study Objectives: To assess the relative bioavailability of crystalline formulation tablet versus reference amorphous formulation tablet of rilzabrutinib in fasted conditions in healthy male and female participants.

**[00218]** Secondary Study Objectives: To assess the relative bioavailability of crystalline formulation tablet versus reference amorphous formulation tablet of rilzabrutinib in fed conditions in healthy male and female participants; to assess the food effect with crystalline formulation tablet and with reference amorphous formulation tablet of rilzabrutinib in healthy male and female participants; and to assess the safety and tolerability of a single oral 600 mg amorphous dose (reference formulation) and a single oral 500 mg crystalline dose (test

formulation) of rilzabrutinib administered under fed and fasted conditions.

[00219] The scope of the trial is a safety and pharmacokinetics study.

[00220] The four arms of the study are shown in Table 10, below.

Table 10. The four arms of the study.

| Arm Label                                           | Arm description                                                                                                                            | Arm type                      |
|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Treatment A:<br>rilzabrutinib<br>amorphous fasted   | Participants will receive single oral dose of amorphous tablet formulation rilzabrutinib under fasted conditions on Day 1 for one period   | Active Comparator / Reference |
| Treatment B:<br>rilzabrutinib<br>crystalline fasted | Participants will receive single oral dose of crystalline tablet formulation rilzabrutinib under fasted conditions on Day 1 for one period | Experimental / Test           |
| Treatment C:<br>rilzabrutinib<br>amorphous fed      | Participants will receive single oral dose of amorphous tablet formulation rilzabrutinib under fed conditions on Day 1 for one period      | Active Comparator / Reference |
| Treatment D:<br>rilzabrutinib<br>crystalline fed    | Participants will receive single oral dose of crystalline tablet formulation rilzabrutinib under fed conditions on Day 1 for one period    | Experimental / Test           |

[00221] Eligible participants were randomly assigned in Latin square design to receive the following study interventions in 1 of 4 sequences:

[00222] Treatment A: a single oral 600 mg dose of amorphous tablet formulation rilzabrutinib under fasted conditions using 2 x 300 mg tablets (= Reference in fasted condition).

[00223] Treatment B: a single oral 500 mg dose of crystalline tablet formulation rilzabrutinib under fasted conditions using 1 x 500 mg tablet (= Test in fasted condition).

[00224] Treatment C: a single oral 600 mg dose of amorphous tablet formulation rilzabrutinib under fed conditions using 2 x 300 mg tablets (= Reference in fed condition).

[00225] Treatment D: a single oral 500 mg dose of crystalline tablet formulation rilzabrutinib under fed conditions using 1 x 500 mg tablet (= Test in fed condition).

**[00226]** The following sequences were randomly assigned on Day 1 in a 1:1:1:1 ratio:

| Sequence | Period 1 | Period 2 | Period 3 | Period 4 |
|----------|----------|----------|----------|----------|
| 1        | A        | B        | C        | D        |
| 2        | D        | A        | B        | C        |
| 3        | C        | D        | A        | B        |
| 4        | B        | C        | D        | A        |

**[00227]** Each administration of investigational medicinal product (IMP) was separated by a washout process with a duration of 2 days (1 day of treatment at a single dose was followed by 1 day washout).

**[00228]** The end of the trial was the last visit of the last participant (LSLV).

**[00229]** Study Population: Healthy volunteers, all genders, minimum age of 18 years and maximum age of 55 years. Number of participants (planned and analyzed): 28 healthy adult male and female participants were randomized to study interventions as planned.

**[00230]** Inclusion Criteria: Body weight between 50.0 and 100.0 kg, inclusive, if male, and between 40.0 and 90.0 kg, inclusive, if female, body mass index (BMI) between 18.0 and 32.0 kg/m<sup>2</sup>, inclusive. Willing to abstain from using tobacco or nicotine-containing products or consuming alcohol from check-in (Day -1) until discharge at end-of-study visit. Willing to abstain from taking any prescription drugs, dietary supplements, or non-prescription drugs within 14 days or 5 half-lives, whichever, is longer, prior to the first dose of study drug through the follow-up phone call. Use of hormonal contraception and aspirin (at doses of  $\leq 2000$  mg/day) or ibuprofen (at doses of  $\leq 1200$  mg/day) are allowed prior to and during the study. Negative urine drug/alcohol testing at screening and check-in (Day -1). Screening urine drug/alcohol testing may be repeated once if deemed appropriate by the site Investigator. Willing to abstain from consuming grapefruit, star fruit, or Seville orange-containing products from 14 days prior to first dose of study drug until discharge from the clinical study unit.

**[00231]** Exclusion Criteria: Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecologic (if female), infectious disease, or signs of acute illness. Participant has clinical signs and symptoms consistent with COVID-19, *e.g.* fever, dry cough, dyspnea, loss of taste and smell, sore throat, fatigue or confirmed infection by appropriate laboratory test within the last 4 weeks prior to Screening. Participant who had severe course of COVID-19 (*i.e.*, hospitalization, extracorporeal membrane

oxygenation [ECMO], mechanically ventilated). Participant has a positive test result for SARS-CoV-2 (measured via Real-time Reverse Transcriptase Polymerase Chain Reaction [RT-PCR] or Rapid Antigen Test [RAT]).

**[00232]** Frequent headaches and/or migraine, recurrent nausea and/or vomiting (for vomiting only: more than twice a month). Blood donation, any volume, within 1 month before inclusion. Symptomatic postural hypotension, irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in systolic blood pressure <30 mmHg within 3 minutes when changing from supine to standing position.

**[00233]** Presence or history of drug hypersensitivity, or allergic disease diagnosed and treated by a physician. Participants with known hypersensitivity to any component of the IMP formulation or allergic disease diagnosed and treated by a physician. History or presence of drug or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis). Regular intake of nicotine (via patch, smoking, vaping or other forms) more than 10 mg per day (based on the average nicotine content of 10-12 mg of nicotine per cigarette and inhalation of up to 2 mg of nicotine per cigarette), and unable to stop smoking during the study (occasional smoker can be enrolled). Excessive consumption of beverages containing xanthine bases (more than 4 cups or glasses per day). If female, pregnancy (defined as positive  $\beta$ -HCG blood test), or breast-feeding.

**[00234]** Any medication (including St John's Wort or ginseng) within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic half-life of the medication, with the exception of aspirin/ibuprofen, hormonal contraception, and menopausal hormone replacement therapy. Any vaccination (except COVID-19 vaccination, see below) within the last 28 days and any biologics (antibody or its derivatives) given within 4 months before inclusion. Non-live vaccines, including COVID-19: last administration of a vaccine within 4 weeks before randomization. Live vaccines: last administration of a vaccine within 3 months before randomization.

**[00235]** Positive result on any of the following tests: hepatitis B surface antigen (HBs Ag), anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab). Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates). Positive alcohol breath or alcohol urine test. Positive pregnancy test. Gilbert's Syndrome.

**[00236]** Specific vulnerable populations: Women of child-bearing potential using contraception.

[00237] Interventions. See Table 11, below.

Table 11. Interventions

| INN or placebo or any descriptive name                   | Pharmaceutical form | Route of administration |
|----------------------------------------------------------|---------------------|-------------------------|
| IMP1: Rilzabrutinib; 300 mg amorphous tablet (reference) | Film coated tablet  | Oral                    |
| IMP2: Rilzabrutinib, 500 mg crystalline tablet (test)    | Film coated tablet  | Oral                    |

[00238] Endpoints. See Tables 12-13, below. Primary Endpoints are relative bioavailability as assessed by rilzabrutinib plasma PK parameters following administration of the test and reference formulations in the fasted state, e.g., C<sub>max</sub>, AUC<sub>last</sub>, AUC. Secondary Endpoints are relative bioavailability as assessed by rilzabrutinib plasma PK parameters following administration of the test and reference formulations in the fed state, e. g., C<sub>max</sub>, AUC<sub>last</sub>, AUC; food effects as assessed by rilzabrutinib plasma PK parameters following administration of the test and reference formulations under the fed versus fasted state, e. g., C<sub>max</sub>, AUC<sub>last</sub>, AUC; and safety of reference and test formulations as assessed by physical examinations, vital signs, 12 lead ECGs, clinical laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis), and adverse events.

[00239] Abbreviations: AUC = area under the plasma concentration versus time curve extrapolated to infinity; AUC<sub>last</sub> = area under the plasma concentration versus time curve from time zero to the last measurable concentration; C<sub>max</sub> = maximum plasma concentration; ECG = electrocardiogram; PK = pharmacokinetic.

Table 12. Primary Endpoints

| Endpoint title           | Endpoint Description | Time frame for evaluation |
|--------------------------|----------------------|---------------------------|
| <b>Primary Endpoints</b> |                      |                           |

|                                                                                                                                                                      |                                                                                                                                 |                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------|
| Relative bioavailability as assessed by rilzabrutinib $C_{\max}$ following administration of the test and reference formulations in the <b>fasted</b> state          | $C_{\max}$ : maximum plasma concentration                                                                                       | Day 1 to Day 8 |
| Relative bioavailability as assessed by rilzabrutinib $AUC_{\text{last}}$ following administration of the test and reference formulations in the <b>fasted</b> state | $AUC_{\text{last}}$ : area under the plasma concentration versus time curve from time zero to the last measurable concentration | Day 1 to Day 8 |
| Relative bioavailability as assessed by rilzabrutinib AUC following administration of the test and reference formulations in the <b>fasted</b> state                 | AUC: area under the plasma concentration versus time curve extrapolated to infinity                                             | Day 1 to Day 8 |

Table 13. Secondary Endpoints

| Secondary Endpoints                                                                                                                                               |                                                                                                                                 |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------|
| Relative bioavailability as assessed by rilzabrutinib $C_{\max}$ following administration of the test and reference formulations in the <b>fed</b> state          | $C_{\max}$ : maximum plasma concentration                                                                                       | Day 1 to Day 8 |
| Relative bioavailability as assessed by rilzabrutinib $AUC_{\text{last}}$ following administration of the test and reference formulations in the <b>fed</b> state | $AUC_{\text{last}}$ : area under the plasma concentration versus time curve from time zero to the last measurable concentration | Day 1 to Day 8 |
| Relative bioavailability as assessed by rilzabrutinib AUC following administration of the test and reference formulations in the <b>fed</b> state                 | AUC: area under the plasma concentration versus time curve extrapolated to infinity                                             | Day 1 to Day 8 |
| Food effects as assessed by rilzabrutinib $C_{\max}$ following administration of the test and reference formulations under the fed versus fasted state            | $C_{\max}$ : maximum plasma concentration                                                                                       | Day 1 to Day 8 |

|                                                                                                                                                                 |                                                                                                                                                                               |                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Food effects as assessed by rilzabrutinib AUC <sub>last</sub> following administration of the test and reference formulations under the fed versus fasted state | AUC <sub>last</sub> : area under the plasma concentration versus time curve from time zero to the last measurable concentration                                               | Day 1 to Day 8 |
| Food effects as assessed by rilzabrutinib AUC following administration of the test and reference formulations under the fed versus fasted state                 | AUC: area under the plasma concentration versus time curve extrapolated to infinity                                                                                           | Day 1 to Day 8 |
| Safety of reference and test formulations                                                                                                                       | As assessed by physical examinations, vital signs, 12 lead ECGs, clinical laboratory tests (clinical chemistry, hematology, coagulation, and urinalysis), and adverse events. | Day 1 to Day 8 |

**[00240]** Statistical methods. Statistical considerations.

**[00241]** Primary endpoint: Pharmacokinetic. Relative bioavailability (Frel) of crystalline formulation compared to amorphous formulation in fasted condition was assessed for maximum plasma concentration (C<sub>max</sub>), AUC until last timepoint with quantifiable concentration (AUC<sub>last</sub>), and area under plasma concentration versus time curve extrapolated to infinity (AUC) using a linear model on log-transformed parameters, with and without dose normalization. Formulation ratios (geometric mean ratios) were estimated from the model, as well as 90% confidence intervals (CIs).

**[00242]** Main secondary endpoints.

**[00243]** Pharmacokinetic. Relative bioavailability of crystalline formulation compared to amorphous formulation in fed condition (with and without dose normalization) and food effect for each formulation were assessed for C<sub>max</sub>, AUC<sub>last</sub> and AUC using a linear model on log-transformed parameters. The test/reference ratios of PK parameters after log transformation (geometric mean ratios) for the different formulation and food conditions were estimated, as well as the 90% CIs.

**[00244]** Safety. Secondary endpoints were adverse events (AEs), laboratory parameters, vital signs, and electrocardiograms (ECGs). Analyses were based on the review of individual values, and descriptive statistics. The safety analysis focused on the treatment-emergent (TE) period, defined as the time from the first IMP administration of a study period up to the next study period (excluded) or up to the end of study visit (included) for the last study period. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Their

severities were graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The numbers (%) of participants experiencing treatment emergent adverse events (TEAEs) were summarized. Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results, vital signs, and ECG were flagged and summarized using frequency tables.

**[00245]** Summary of results.

**[00246]** Participant Disposition: A total of 28 participants were randomized and exposed to rilzabrutinib in one of four treatment sequences (ABCD, BCDA, CDAB, or DABC). 27 of 28 participants completed the study while one participant withdrew consent on day 6 for personal reasons (sequence randomized ABCD, not exposed to D).

**[00247]** Analysis Populations: All participants (N=28) were evaluable for safety assessment and PK parameters.

**[00248]** Demographic and other baseline characteristics: 18 of 28 (64.3%) participants were male, 10 of 28 (35.7%) participants were female, the median (min-max) age at enrollment was 31.5 (19-53) years.

**[00249]** Exposure: All except one participant (27 of 28) received four, single doses of rilzabrutinib: 600 mg amorphous formulation (reference formulation) in the fed and fasted states as well as single doses of 500 mg crystalline formulation (test formulation) in the fed and fasted states. One subject withdrew from the study prior to completion of treatment sequence 1 and received single doses of 600 mg amorphous formulation in the fed and fasted states as well as a 500 mg crystalline formulation in the fasted state. This participant was not replaced.

**[00250]** Safety results: The administration of rilzabrutinib in both formulations was safe and well tolerated. Overall, 21 of 28 (75%) participants experienced a total of 60 AEs (58 TEAEs and 2 post-treatment AEs). 41 of 58 (70.6%) reported TEAEs were gastrointestinal in nature. There were no deaths, serious adverse events (SAEs), or withdrawals from the study due to TEAEs.

**[00251]** No other clinically significant vital sign changes, ECG changes, or alterations in laboratory parameters were observed.

**[00252]** The most common TEAEs for subjects most recently receiving both the amorphous and crystalline formations were gastrointestinal in nature.

**[00253]** Following amorphous formulation in the fasted state (A), 15 of 28 (53.6%) participants reported 20 gastrointestinal TEAEs including 8 of Grade 1 diarrhea, 4 of Grade 1 nausea, 2 of Grade 1 abdominal pain, 1 of Grade 1 vomiting, and 1 of Grade 1 dyspepsia. One participant reported Grade 2 nausea and Grade 2 abdominal pain; one participant reported Grade

2 nausea; and one participant reported Grade 2 diarrhea. All TEAEs resolved without treatment beyond increased oral fluids.

**[00254]** Following crystalline formulation in the fasted state (B), 11 of 28 (39.3%) participants reported 14 gastrointestinal TEAEs including 8 of Grade 1 diarrhea, 4 of Grade 1 nausea, 1 of Grade 1 abdominal pain, and 1 of Grade 1 flatulence. All TEAEs resolved without treatment.

**[00255]** Gastrointestinal TEAEs were less frequent for each formulation in the fed state: following amorphous formulation (C), 4 of 28 (14.3%) participants reported 3 Grade 1 nausea and 1 Grade 1 abdominal pain and following crystalline formulation (D), 3 of 27 (11.1%) participants reported 2 Grade 1 nausea and 1 Grade 1 diarrhea.

**[00256]** Pharmacokinetic results. A total of 28 participants were included in the PK analysis population. One participant discontinued early and so had no data for the “500 mg crystalline Fed” study intervention.

**[00257]** Mean rilzabrutinib plasma concentration-time profiles following single SC doses are shown in Figure 1 (linear scale) and Figure 2 (semi-logarithmic scale). A summary of plasma PK parameters of rilzabrutinib following a single oral dose of 500 mg crystalline or 600 mg amorphous rilzabrutinib in fasted or fed condition is shown in Table 14.

Table 14. Mean  $\pm$ SD (geometric mean) [CV%] pharmacokinetic parameters for rilzabrutinib following single oral administration of two formulations in healthy participants in fasted or fed conditions.

| <b>PK Parameters</b>                 | <b>500 mg<br/>Crystalline<br/>Fasted</b>  | <b>500 mg<br/>Crystalline Fed</b> | <b>600 mg<br/>Amorphous<br/>Fasted</b>   | <b>600 mg<br/>Amorphous<br/>Fed</b> |
|--------------------------------------|-------------------------------------------|-----------------------------------|------------------------------------------|-------------------------------------|
| N                                    | 28                                        | 27                                | 28                                       | 28                                  |
| C <sub>max</sub><br>(mg/mL)          | 212 $\pm$ 192 (154)<br>[90]               | 170 $\pm$ 124 (140)<br>[73]       | 220 $\pm$ 144 (179)<br>[66]              | 182 $\pm$ 123 (152)<br>[68]         |
| C <sub>max</sub> /Dose<br>(ng/mL/mg) | 0.425 $\pm$ 0.384<br>(0.309) [90]         | 0.340 $\pm$ 0.248<br>(0.280) [73] | 0.366 $\pm$ 0.240<br>(0.298) [66]        | 0.304 $\pm$ 0.206<br>(0.253) [68]   |
| AUC<br>(ng h/mL)                     | 689 $\pm$ 756 (509)<br>[110] <sup>b</sup> | 524 $\pm$ 353 (445)<br>[67]       | 715 $\pm$ 483 (569)<br>[68] <sup>c</sup> | 608 $\pm$ 343 (525)<br>[56]         |
| AUC/Dose<br>(ng h/mL/mg)             | 1.38 $\pm$ 1.51                           | 1.05 $\pm$ 0.705<br>(0.889) [67]  | 1.19 $\pm$ 0.805                         | 1.01 $\pm$ 0.572<br>(0.876) [56]    |

|                                   |                                         |                              |                                           |                              |
|-----------------------------------|-----------------------------------------|------------------------------|-------------------------------------------|------------------------------|
|                                   | (1.02) [110] <sup>b</sup>               |                              | (0.948) [68] <sup>c</sup>                 |                              |
| AUClast<br>(ng h/mL)              | 648 ± 741 (457)<br>[114]                | 523 ± 352 (443)<br>[67]      | 699 ± 477 (555)<br>[68]                   | 607 ± 343 (524)<br>[56]      |
| AUClast/Dose<br>(ng h/mL/mg)      | 1.30 ± 1.48<br>(0.914) [114]            | 1.05 ± 0.704<br>(0.887) [67] | 1.17 ± 0.796<br>(0.925) [68]              | 1.01 ± 0.571<br>(0.873) [56] |
| t <sub>max</sub> <sup>a</sup> (h) | 1.50 (1.00, 4.00)                       | 2.50 (1.00, 5.00)            | 1.50 (1.00, 5.00)                         | 2.50 (1.00, 5.00)            |
| t <sub>1/2z</sub> (h)             | 3.02 ± 1.09<br>(2.84) [36] <sup>b</sup> | 2.74 ± 0.641<br>(2.66) [23]  | 3.21 ± 1.18<br>(3.03) [37] <sup>c</sup>   | 2.66 ± 0.520<br>(2.60) [20]  |
| CL/F (L/h)                        | 1290 ± 1130<br>(983) [88] <sup>b</sup>  | 1300 ± 739<br>(1120) [57]    | 1420 ± 1550<br>(1060) [109] <sup>c</sup>  | 1330 ± 765<br>(1140) [58]    |
| V <sub>z</sub> /F (L)             | 170 ± 9540<br>(4030) [155] <sup>b</sup> | 4880 ± 2360<br>(4320) [48]   | 7800 ± 13500<br>(4610) [173] <sup>c</sup> | 4900 ± 2610<br>(4290) [53]   |

a Median (Min, Max)

b N=26. For 2 participants in “500 mg Crystalline Fasted”, log linear terminal phase was not characterized sufficiently.

c N=27. For 1 participant in “600 mg Amorphous Fasted”, log linear terminal phase was not characterized sufficiently.

**[00258]** Summaries of the geometric mean ratios and 90% CIs for the primary PK parameters are shown in Table 15 and Table 16, with the latter presenting dose-normalized PK parameters.

Table 15 - Primary analysis - Relative bioavailability and food effect - Point estimates of treatment ratio with 90% confidence intervals for rilzabrutinib C<sub>max</sub>, AUClast and AUC - PK population

| Comparison                        | Parameter              | Point Estimate | 90% CI         |
|-----------------------------------|------------------------|----------------|----------------|
| Treatment B versus<br>Treatment A | Log(C <sub>max</sub> ) | 0.93           | (0.73 to 1.19) |
|                                   | Log(AUClast)           | 0.86           | (0.68 to 1.08) |
|                                   | Log(AUC)               | 0.85           | (0.69 to 1.05) |
| Treatment D versus<br>Treatment C | Log(C <sub>max</sub> ) | 0.83           | (0.65 to 1.07) |
|                                   | Log(AUClast)           | 0.82           | (0.65 to 1.03) |

|                                   |              |      |                |
|-----------------------------------|--------------|------|----------------|
|                                   | Log(AUC)     | 0.85 | (0.69 to 1.04) |
| Treatment C versus<br>Treatment A | Log(Cmax)    | 0.86 | (0.65 to 1.14) |
|                                   | Log(AUClast) | 0.95 | (0.73 to 1.23) |
|                                   | Log(AUC)     | 0.85 | (0.67 to 1.07) |
| Treatment D versus<br>Treatment B | Log(Cmax)    | 0.77 | (0.58 to 1.02) |
|                                   | Log(AUClast) | 0.90 | (0.69 to 1.18) |
|                                   | Log(AUC)     | 0.85 | (0.67 to 1.07) |

Treatment A: Rilzabrutinib 600 mg Amorphous, Fasted. Treatment B: Rilzabrutinib 500 mg Crystalline, Fasted. Treatment C: Rilzabrutinib 600 mg Amorphous, Fed. Treatment D: Rilzabrutinib 500 mg Crystalline, Fed.

CI: confidence interval

In primary analysis, all available PK parameters were included.

Table 16 - Primary analysis - Relative bioavailability and food effect of Rilzabrutinib Cmax, AUClast and AUC - Point estimates of treatment ratio with 90% confidence intervals for dose normalized PK parameters - PK population

| Comparison                        | Parameter                    | Point Estimate | 90% CI         |
|-----------------------------------|------------------------------|----------------|----------------|
| Treatment B versus<br>Treatment A | Log (Dose Normalized Cmax)   | 1.12           | (0.88 to 1.43) |
|                                   | Log(Dose Normalized AUClast) | 1.03           | (0.82 to 1.29) |
|                                   | Log(Dose Normalized AUC)     | 1.02           | (0.83 to 1.26) |
| Treatment D versus<br>Treatment C | Log (Dose Normalized Cmax)   | 1.00           | (0.78 to 1.28) |
|                                   | Log(Dose Normalized AUClast) | 0.98           | (0.78 to 1.24) |
|                                   | Log(Dose Normalized AUC)     | 1.02           | (0.83 to 1.25) |
| Treatment C versus<br>Treatment A | Log (Dose Normalized Cmax)   | 0.86           | (0.65 to 1.14) |
|                                   | Log(Dose Normalized AUClast) | 0.95           | (0.73 to 1.23) |
|                                   | Log(Dose Normalized AUC)     | 0.85           | (0.67 to 1.07) |
| Treatment D versus<br>Treatment B | Log (Dose Normalized Cmax)   | 0.77           | (0.58 to 1.02) |
|                                   | Log(Dose Normalized AUClast) | 0.90           | (0.69 to 1.18) |
|                                   | Log(Dose Normalized AUC)     | 0.85           | (0.67 to 1.07) |

Treatment A: Rilzabrutinib 600 mg Amorphous, Fasted. Treatment B: Rilzabrutinib 500 mg

Crystalline, Fasted. Treatment C: Rilzabrutinib 600 mg Amorphous, Fed. Treatment D: Rilzabrutinib 500 mg Crystalline, Fed.

CI: confidence interval

In primary analysis, all available PK parameters were included.

**[00259]** In fasted condition, exposure was similar in term of C<sub>max</sub> and slightly higher in term of AUC for 600 mg amorphous rilzabrutinib compared to 500 mg crystalline rilzabrutinib (Table 14), with test/reference ratios of 0.93 (90% CI: 0.73 to 1.19) and 0.85 (90% CI: 0.69 to 1.05), respectively (Table 15). In fed condition, exposure was slightly higher in term of C<sub>max</sub> and AUC for 600 mg amorphous rilzabrutinib compared to 500 mg crystalline rilzabrutinib (Table 14), with test/reference ratios of 0.83 (90% CI: 0.65 to 1.07) and 0.85 (90% CI: 0.69 to 1.04), respectively (Table 15).

**[00260]** The dose-normalized exposures were similar between both formulations, indicating similar bioavailability for the formulations after adjustment for dose differences (Table 16). Point estimates (90% CI) for dose-normalized crystalline/amorphous ratios were 1.12 (90% CI: 0.88 to 1.43) and 1.02 (90% CI: 0.83 to 1.26) in fasted condition, and 1.00 (90% CI: 0.78 to 1.28) and 1.02 (90% CI: 0.83 to 1.25) in the fed condition, for C<sub>max</sub> and AUC, respectively. All 90% CIs of the ratio of the geometric means included 1 (Table 15 and Table 16).

**[00261]** Following oral administration of 500 mg crystalline or 600 mg amorphous rilzabrutinib in fasted condition, median t<sub>max</sub> of rilzabrutinib was similar (1.50 h). Median t<sub>max</sub> was delayed when rilzabrutinib was administered in fed condition but was similar for the two formulations (2.50 h). Mean t<sub>1/2z</sub> of rilzabrutinib appeared similar between 500 mg crystalline or 600 mg amorphous rilzabrutinib in fasted or fed condition, with mean values ranging between 2.66 and 3.21 hours.

**[00262]** For both formulations, exposure, in term of C<sub>max</sub> and AUC, was lower when rilzabrutinib was administered in fed condition than when administered in fasted condition (Table 14). Point estimates for fed/fasted ratios were 0.77 (90% CI: 0.58 to 1.02) and 0.85 (90% CI: 0.67 to 1.07) for the 500 mg crystalline, and 0.86 (90% CI: 0.65 to 1.14) and 0.85 (90% CI: 0.67 to 1.07) for the 600 mg amorphous rilzabrutinib, for C<sub>max</sub> and AUC, respectively (Table 15).

**[00263]** Total variability (based on CV%) in plasma rilzabrutinib systemic exposure parameters was generally high (56% to 114%) and appeared generally similar between the two formulations, in fasted or fed condition (Table 14).

**[00264]** Conclusions. In the fasted state, the bioavailability of rilzabrutinib following a single dose of the 500 mg crystalline tablet formulation was similar to the 600 mg amorphous tablet formulation after dose normalization. For both formulations, a high fat meal resulted in an average of 15% reduction of exposure (AUC) in comparison to fasted condition.

**[00265]** Overall, rilzabrutinib given as single doses of 600 mg amorphous formulation and 500 mg crystalline formulation in the fasted and fed states was safe and well tolerated in healthy participants. Gastrointestinal adverse events were common and observed more often in the fasted state and with amorphous formulation.

**[00266] Example 8: Additional Crystalline Formulation (600 mg)**

**[00267]** A formulation for immediate release film-coated tablets containing 600 mg of crystalline Form B rilzabrutinib was prepared. The tablets were prepared for oral administration and are white to off-white oblong film-coated tablets. The components for this formulation are listed in Table 17, below.

Table 17. Composition of 600 mg crystalline rilzabrutinib tablet formulation

| Component                               | Unit weight<br>(mg/tablet) | Percentage<br>(w/w) | Function       |
|-----------------------------------------|----------------------------|---------------------|----------------|
| <b>Intragranular</b>                    |                            |                     |                |
| Crystalline rilzabrutinib               | 600.00                     | 65.00               | drug substance |
| Microcrystalline Cellulose <sup>a</sup> | 234.92                     | 25.45               | diluent        |
| Colloidal anhydrous<br>silicon dioxide  | 8.31                       | 0.90                | glidant        |
| Crospovidone Type A                     | 18.46                      | 2.00                | disintegrant   |
| Magnesium Stearate                      | 2.31                       | 0.25                | lubricant      |
| <b>Extragranular</b>                    |                            |                     |                |
| Microcrystalline Cellulose              | 46.15                      | 5.00                | diluent        |
| Colloidal anhydrous<br>silicon dioxide  | 3.69                       | 0.40                | glidant        |
| Magnesium Stearate                      | 9.23                       | 1.00                | lubricant      |
| <b>Core tablet mass</b>                 | 923.08                     | 100.00              |                |
| <b>Film-coating</b>                     |                            |                     |                |

|                                                         |        |                   |                          |
|---------------------------------------------------------|--------|-------------------|--------------------------|
| White ready-to-use<br>film-coating agent <sup>c,d</sup> | 27.69  | 3.00 <sup>b</sup> | film-coating<br>material |
| <b>Film-coated tablet mass</b>                          | 950.77 |                   |                          |

a The microcrystalline cellulose amount was adjusted to compensate for rilzabrutinib drug substance weight.

b Represents 3% weight gain on the core tablet mass.

c Ready to use Opadry® II 32F38977 composed of 36% lactose monohydrate, 28% hypromellose (15 mPa.s), 26% titanium dioxide (E171) and 10% macrogol 3000-polyethylene glycol 3000.

d Film-coating agent was prepared as a water suspension for spraying with purified water. Water is considered as a processing agent and is removed during the process.

**[00268]** Although the present disclosure has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated herein in their entirety by reference.

**[00269]** Embodiments:

**[00270]** Non-limiting embodiments of the disclosure include:

**[00271]** Embodiment 1. A tablet comprising: at least one compound chosen from (2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile (the compound of Formula (I)), and pharmaceutically acceptable salts thereof; at least one diluent; at least one disintegrant; at least one lubricant; and optionally, at least one glidant.

**[00272]** Embodiment 2. The tablet of Embodiment 1, wherein the tablet comprises an intragranular phase and an extragranular phase.

**[00273]** Embodiment 3. The tablet of Embodiment 1 or Embodiment 2, wherein the at least one diluent is chosen from lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, calcium phosphate, hydroxypropylmethylcellulose, sucrose, calcium sulfate, calcium lactate, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, kaolin, sodium chloride, inositol, and bentonite.

**[00274]** Embodiment 4. The tablet of Embodiment 3, wherein the at least one diluent comprises microcrystalline cellulose.

[00275] Embodiment 5. The tablet of Embodiment 3, wherein the at least one diluent is chosen from microcrystalline cellulose 50  $\mu\text{m}$ , microcrystalline cellulose 90  $\mu\text{m}$ , and microcrystalline cellulose 180  $\mu\text{m}$ .

[00276] Embodiment 6. The tablet of Embodiment 3, wherein the at least one diluent is present in a total amount ranging from about 75 mg to about 400 mg.

[00277] Embodiment 7. The tablet of Embodiment 3, wherein the at least one diluent is present in a total amount ranging from about 10% to about 50% by weight.

[00278] Embodiment 8. The tablet of Embodiment 7, wherein the at least one diluent is present in the intragranular phase in a total amount ranging from about 15% to about 45% by weight.

[00279] Embodiment 9. The tablet of Embodiment 7 or Embodiment 8, wherein the at least one diluent is present in the extragranular phase in a total amount ranging from about 0% to about 15% by weight.

[00280] Embodiment 10. The tablet of Embodiment 1 or Embodiment 2, wherein the at least one glidant is chosen from colloidal silicon dioxide and talc.

[00281] Embodiment 11. The tablet of Embodiment 10, wherein the at least one glidant comprises at least one of colloidal silicon dioxide having an average specific surface area of about 200  $\text{m}^2/\text{g}$ , and colloidal silicon dioxide having an average specific surface area of about 300  $\text{m}^2/\text{g}$ .

[00282] Embodiment 12. The tablet of Embodiment 10, wherein the at least one glidant is present in a total amount ranging from 0 mg to about 50 mg.

[00283] Embodiment 13. The tablet of Embodiment 10, wherein the at least one glidant is present in a total amount ranging from about 0% to about 5% by weight.

[00284] Embodiment 14. The tablet of Embodiment 13, wherein the at least one glidant is present in the intragranular phase in a total amount ranging from about 0% to about 5% by weight.

[00285] Embodiment 15. The tablet of Embodiment 13, wherein the at least one glidant is present in the extragranular phase in a total amount ranging from about 0% to about 5% by weight.

[00286] Embodiment 16. The tablet of Embodiment 1 or Embodiment 2, wherein the at least one disintegrant is chosen from a starch, a cross-linked starch, a cellulose, a cross-linked cellulose, a cross-linked polymer, an alginate, a clay, a gum, a glycolate, bentonite, a natural sponge, a surfactant, a resin, citrus pulp, and sodium lauryl sulfate.

[00287] Embodiment 17. The tablet of Embodiment 16, wherein the at least one

disintegrant is chosen from cross linked polyvinyl N-pyrrolidone (crospovidone) and cross linked carboxymethyl cellulose (croscarmellose).

**[00288]** Embodiment 18. The tablet of Embodiment 16, wherein the at least one disintegrant is present in a total amount ranging from 1 mg to about 125 mg.

**[00289]** Embodiment 19. The tablet of Embodiment 16, wherein the at least one disintegrant is present in a total amount ranging from about 0.1% to about 15% by weight.

**[00290]** Embodiment 20. The tablet of Embodiment 19, wherein the at least one disintegrant is present in the intragranular phase in a total amount ranging from about 0.1% to about 10% by weight.

**[00291]** Embodiment 21. The tablet of Embodiment 19, wherein the at least one disintegrant is present in the extragranular phase in a total amount ranging from about 0% to about 10% by weight.

**[00292]** Embodiment 22. The tablet of Embodiment 1 or Embodiment 2, wherein the at least one lubricant is chosen from stearic acid, calcium hydroxide, talc, a hydrocarbon, a hydrogenated vegetable oil, higher fatty acids, a stearate, glycerol, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol, a methoxypolyethylene glycol, sodium oleate, sodium benzoate, glyceryl behenate, magnesium or sodium lauryl sulfate, colloidal silica, a starch, silicone oil, and a surfactant.

**[00293]** Embodiment 23. The tablet of Embodiment 22, wherein the at least one lubricant is chosen from magnesium stearate and sodium stearyl fumarate.

**[00294]** Embodiment 24. The tablet of Embodiment 22, wherein the at least one lubricant is present in a total amount ranging from 0.1 mg to about 50 mg.

**[00295]** Embodiment 25. The tablet of Embodiment 22, wherein the at least one lubricant is present in a total amount ranging from about 0.01% to about 5% by weight.

**[00296]** Embodiment 26. The tablet of Embodiment 25, wherein the at least one lubricant is present in the intragranular phase in a total amount ranging from about 0.1% to about 5% by weight.

**[00297]** Embodiment 27. The tablet of Embodiment 25, wherein the at least one lubricant is present in the extragranular phase in a total amount ranging from about 0% to about 5% by weight.

**[00298]** Embodiment 28. The tablet of Embodiment 2, wherein the intragranular phase comprises at least one compound chosen from (2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile (the compound of Formula (I)), and pharmaceutically

acceptable salts thereof, at least one diluent, at least one disintegrant, and at least one lubricant.

[00299] Embodiment 29. The tablet of Embodiment 28, wherein the at least one diluent comprises microcrystalline cellulose 50  $\mu\text{m}$ .

[00300] Embodiment 30. The tablet of Embodiment 28, wherein the at least one lubricant comprises magnesium stearate.

[00301] Embodiment 31. The tablet of Embodiment 28, wherein the at least one lubricant comprises sodium stearyl fumarate.

[00302] Embodiment 32. The tablet of Embodiment 28, wherein the at least one disintegrant comprises cross linked polyvinyl N-pyrrolidone (crospovidone).

[00303] Embodiment 33. The tablet of Embodiment 28, wherein the intragranular phase further comprises at least one glidant.

[00304] Embodiment 34. The tablet of Embodiment 33, wherein the at least one glidant comprises at least one of colloidal silicon dioxide having an average specific surface area of about 200  $\text{m}^2/\text{g}$  and colloidal silicon dioxide having an average specific surface area of about 300  $\text{m}^2/\text{g}$ .

[00305] Embodiment 35. The tablet of Embodiment 2, wherein the extragranular phase comprises at least one lubricant.

[00306] Embodiment 36. The tablet of Embodiment 35, wherein the at least one lubricant comprises magnesium stearate.

[00307] Embodiment 37. The tablet of Embodiment 35, wherein the at least one lubricant comprises sodium stearyl fumarate.

[00308] Embodiment 38. The tablet of Embodiment 35, wherein the extragranular phase further comprises at least one diluent.

[00309] Embodiment 39. The tablet of Embodiment 38, wherein the at least one diluent comprises microcrystalline cellulose 180  $\mu\text{m}$ .

[00310] Embodiment 40. The tablet of Embodiment 35, wherein the extragranular phase further comprises at least one glidant.

[00311] Embodiment 41. The tablet of Embodiment 40, wherein the at least one glidant comprises at least one of colloidal silicon dioxide having an average specific surface area of about 200  $\text{m}^2/\text{g}$  and colloidal silicon dioxide having an average specific surface area of about 300  $\text{m}^2/\text{g}$ .

[00312] Embodiment 42. The tablet of Embodiment 35, wherein the extragranular phase further comprises at least one disintegrant.

[00313] Embodiment 43. The tablet of Embodiment 42, wherein the at least one

disintegrant comprises cross linked polyvinyl N-pyrrolidone (crospovidone).

**[00314]** Embodiment 44. The tablet of any one of the preceding Embodiments, wherein the compound of Formula (I) comprises an amorphous form.

**[00315]** Embodiment 45. The tablet of any one of Embodiments 1-43, wherein the compound of Formula (I) is present in at least 50% crystalline form, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, 99.5%, or 100% crystalline.

**[00316]** Embodiment 46. The tablet of Embodiment 45, wherein the compound of Formula (I) comprises crystalline Form B.

**[00317]** Embodiment 47. The tablet of any one of the preceding Embodiments, wherein the compound of Formula (I) is present in an amount ranging from about 200 mg to about 650 mg.

**[00318]** Embodiment 48. The tablet of any one of the preceding Embodiments, wherein the compound of Formula (I) is present in an amount of about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, about 600 mg, about 610 mg, about 620 mg, about 630 mg, about 640 mg, or about 650 mg.

**[00319]** Embodiment 49. The tablet of Embodiment 48, wherein the compound of Formula (I) is present in an amount of about 300 mg.

**[00320]** Embodiment 50. The tablet of Embodiment 48, wherein the compound of Formula (I) is present in an amount of about 500 mg.

**[00321]** Embodiment 51. The tablet of Embodiment 48, wherein the compound of Formula (I) is present in an amount of about 600 mg.

**[00322]** Embodiment 52. The tablet of any one of the preceding Embodiments, wherein the compound of Formula (I) is present in an amount of about 40% to about 75% by weight.

**[00323]** Embodiment 53. The tablet of Embodiment 52, wherein the compound of Formula (I) is present in an amount of about 50% by weight.

**[00324]** Embodiment 54. The tablet of Embodiment 52, wherein the compound of Formula (I) is present in an amount of about 65% by weight.

**[00325]** Embodiment 55. The tablet of Embodiment 52, wherein the compound of

Formula (I) is present in the intragranular phase.

[00326] Embodiment 56. The tablet of any one of the preceding Embodiments, further comprising at least one coating layer.

[00327] Embodiment 57. The tablet of Embodiment 56, wherein the coating layer comprises a taste masking agent.

[00328] Embodiment 58. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide.

[00329] Embodiment 59. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide.

[00330] Embodiment 60. The tablet of Embodiment 58 or 59, wherein the tablet comprises an intragranular phase and an extragranular phase.

[00331] Embodiment 61. The tablet of Embodiment 60, wherein the intragranular phase comprises about 65% by weight of the compound of Formula (I), about 31% by weight microcrystalline cellulose, about 2% by weight crospovidone, about 0.25% by weight magnesium stearate, and about 1% by weight colloidal silicon dioxide.

[00332] Embodiment 62. The tablet of Embodiment 60, wherein the extragranular phase comprises about 1% by weight magnesium stearate.

[00333] Embodiment 63. The tablet of any one of Embodiments 58-62, wherein the compound of Formula (I) is present in an amount of about 270 mg.

[00334] Embodiment 64. The tablet of any one of Embodiments 59-63, wherein the compound of Formula (I) comprises a crystalline form, and preferably comprises crystalline Form B.

[00335] Embodiment 65. The tablet of any one of Embodiments 59-63, wherein the compound of Formula (I) comprises an amorphous form.

[00336] Embodiment 66. The tablet of Embodiment 1, wherein the tablet comprises: about 45% to about 55% by weight amorphous compound of Formula (I), about 35% to about 40% by weight microcrystalline cellulose, about 5% to about 15% by weight crospovidone, and about 0.5% to about 5% by weight sodium stearyl fumarate.

[00337] Embodiment 67. The tablet of Embodiment 1, wherein the tablet comprises: about 45% to about 55% by weight of the compound of Formula (I), about 35% to about 40% by weight microcrystalline cellulose, about 5% to about 15% by weight crospovidone, and about 0.5% to about 5% by weight sodium stearyl fumarate.

[00338] Embodiment 68. The tablet of Embodiment 66 or 67, wherein the tablet comprises an intragranular phase and an extragranular phase.

[00339] Embodiment 69. The tablet of Embodiment 68, wherein the intragranular phase comprises about 50% by weight of the compound of Formula (I), about 38% by weight microcrystalline cellulose, about 10% by weight crospovidone, and about 2% by weight sodium stearyl fumarate.

[00340] Embodiment 70. The tablet of Embodiment 68, wherein the extragranular phase comprises about 5% by weight crospovidone and about 1% by weight sodium stearyl fumarate.

[00341] Embodiment 71. The tablet of any one of Embodiments 66-70, wherein the compound of Formula (I) is present in an amount of about 300 mg or about 400 mg.

[00342] Embodiment 72. The tablet of any one of Embodiments 67-71, wherein the compound of Formula (I) comprises a crystalline form, and preferably comprises crystalline Form B.

[00343] Embodiment 73. The tablet of any one of Embodiments 67-71, wherein the compound of Formula (I) comprises an amorphous form.

[00344] Embodiment 74. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight crystalline Form B of the compound of Formula (I), about 20% to about 35% by weight microcrystalline cellulose, about 0.5% to about 10% by weight disintegrant, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide, wherein the disintegrant comprises at least one of crospovidone and croscarmellose.

[00345] Embodiment 75. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight of the compound of Formula (I), about 20% to about 35% by weight microcrystalline cellulose, about 0.5% to about 10% by weight disintegrant, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide, wherein the disintegrant comprises at least one of crospovidone and croscarmellose.

[00346] Embodiment 76. The tablet of Embodiment 74 or 75, wherein the tablet comprises an intragranular phase and an extragranular phase.

[00347] Embodiment 77. The tablet of Embodiment 76, wherein the intragranular phase

comprises about 65% by weight of the compound of Formula (I), about 23% to about 31% by weight microcrystalline cellulose, about 2.0% to about 4.0% by weight disintegrant, about 0.5% to about 1.0% by weight magnesium stearate, and about 0.9% colloidal silicon dioxide.

**[00348]** Embodiment 78. The tablet of Embodiment 76, wherein the extragranular phase comprises about 1.5% by weight microcrystalline cellulose, about 0% to about 2.0% by weight disintegrant, about 0.2% to about 1.0% by weight magnesium stearate, and about 0.4% colloidal silicon dioxide.

**[00349]** Embodiment 79. The tablet of any one of Embodiments 74-78, wherein the compound of Formula (I) is present in an amount of about 400 mg or about 450 mg.

**[00350]** Embodiment 80. The tablet of any one of Embodiments 75-79, wherein the compound of Formula (I) comprises a crystalline form, and preferably comprises crystalline Form B.

**[00351]** Embodiment 81. The tablet of any one of Embodiments 75-79, wherein the compound of Formula (I) comprises an amorphous form.

**[00352]** Embodiment 82. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide.

**[00353]** Embodiment 83. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide.

**[00354]** Embodiment 84. The tablet of Embodiment 82 or 83, wherein the tablet comprises an intragranular phase and an extragranular phase.

**[00355]** Embodiment 85. The tablet of Embodiment 84, wherein the intragranular phase comprises about 65% by weight of the compound of Formula (I), about 31% by weight microcrystalline cellulose, about 2.0% by weight crospovidone, about 0.25% by weight magnesium stearate, and about 0.9% colloidal silicon dioxide.

**[00356]** Embodiment 86. The tablet of Embodiment 84, wherein the extragranular phase comprises about 1.0% by weight magnesium stearate, and about 0.4% colloidal silicon dioxide.

**[00357]** Embodiment 87. The tablet of any one of Embodiments 82-86, wherein the compound of Formula (I) is present in an amount of about 500 mg.

**[00358]** Embodiment 88. The tablet of any one of Embodiments 83-87, wherein the compound of Formula (I) comprises a crystalline form, and preferably comprises crystalline Form B.

**[00359]** Embodiment 89. The tablet of any one of Embodiments 84-87, wherein the compound of Formula (I) comprises an amorphous form.

**[00360]** Embodiment 90. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide.

**[00361]** Embodiment 91. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide.

**[00362]** Embodiment 92. The tablet of Embodiment 90 or 91, wherein the tablet comprises an intragranular phase and an extragranular phase.

**[00363]** Embodiment 93. The tablet of Embodiment 92, wherein the intragranular phase comprises about 65% by weight of the compound of Formula (I), about 30% by weight microcrystalline cellulose, about 2.0% by weight crospovidone, about 0.5% by weight magnesium stearate, and about 0.9% colloidal silicon dioxide.

**[00364]** Embodiment 94. The tablet of Embodiment 92, wherein the extragranular phase comprises about 1.0% by weight magnesium stearate, and about 0.4% colloidal silicon dioxide.

**[00365]** Embodiment 95. The tablet of any one of Embodiments 90-94, wherein the compound of Formula (I) is present in an amount of about 500 mg.

**[00366]** Embodiment 96. The tablet of any one of Embodiments 91-95, wherein the compound of Formula (I) comprises a crystalline form, and preferably comprises crystalline Form B.

**[00367]** Embodiment 97. The tablet of any one of Embodiments 91-95, wherein the compound of Formula (I) comprises an amorphous form.

**[00368]** Embodiment 98. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight of a crystalline compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about

5% by weight colloidal silicon dioxide, wherein the colloidal silicon dioxide comprises at least one of colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g.

**[00369]** Embodiment 99. The tablet of Embodiment 1, wherein the tablet comprises: about 60% to about 70% by weight of a compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide, wherein the colloidal silicon dioxide comprises at least one of colloidal silicon dioxide having an average specific surface area of about 200 m<sup>2</sup>/g and colloidal silicon dioxide having an average specific surface area of about 300 m<sup>2</sup>/g.

**[00370]** Embodiment 100. The tablet of Embodiment 98 or 99, wherein the tablet comprises an intragranular phase and an extragranular phase.

**[00371]** Embodiment 101. The tablet of Embodiment 100, wherein the intragranular phase comprises about 65% by weight of the compound of Formula (I), about 20% to about 30% by weight microcrystalline cellulose, about 2.0% by weight crospovidone, about 0.25% by weight magnesium stearate, and about 0.7 to about 0.9% colloidal silicon dioxide.

**[00372]** Embodiment 102. The tablet of Embodiment 100, wherein the extragranular phase comprises about 1.0% by weight magnesium stearate, about 0% to about 10% microcrystalline cellulose, and about 0.4% to about 0.6% colloidal silicon dioxide.

**[00373]** Embodiment 103. The tablet of any one of Embodiments 98-102, wherein the compound of Formula (I) is present in an amount of about 500 mg.

**[00374]** Embodiment 104. The tablet of any one of Embodiments 98-102, wherein the compound of Formula (I) is present in an amount of about 600 mg.

**[00375]** Embodiment 105. The tablet of any one of Embodiments 99-104, wherein the compound of Formula (I) comprises a crystalline form, and preferably comprises crystalline Form B.

**[00376]** Embodiment 106. The tablet of any one of Embodiments 99-104, wherein the compound of Formula (I) comprises an amorphous form.

**[00377]** Embodiment 107. The tablet of any one of Embodiments 1-43, 45-64, 67-72, 74-80, 82-88, 90-96, and 98-105, wherein the compound of Formula (I) comprises crystalline Form B.

**[00378]** Embodiment 108. The tablet of any one of Embodiments 1-107, further comprising a film-coating agent.

**[00379]** Embodiment 109. The tablet of Embodiment 108, wherein the film coating is

present in an amount of about 2% to about 5% relative to the total weight of the tablet.

[00380] Embodiment 110. The tablet of Embodiment 109, wherein the film coating is present in an amount of about 3% relative to the total weight of the tablet.

[00381] Embodiment 111. A method of treating a disease or condition mediated by BTK in a patient in need thereof, comprising administering to the patient the tablet of any one of Embodiments 1 to 110.

[00382] Embodiment 112. The method of Embodiment 111, wherein the disease or condition mediated by BTK is chosen from at least one of acne, allergy, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson syndrome, toxic epidermal necrolysis (TEN), pemphigus vulgaris, pemphigus foliaceus, ankylosing spondylitis, antiphospholipid antibody syndrome, vasculitis, Guillain-Barre syndrome, scleroderma, Wegener's granulomatosis, psoriasis, granulomatosis with polyangiitis, thrombotic thrombocytopenic purpura, polyarteritis nodosa, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, asthma, moderate-to-severe asthma, mild asthma, moderate asthma, severe asthma, asthma that is not well controlled, autoimmune hepatitis, Behcet's disease, Grave's disease, nephritis, pancreatitis, primary biliary cirrhosis, ulcerative colitis, colitis, conjunctivitis, dermatitis, atopic dermatitis, drug eruptions, drug-induced thrombocytopenia (DITP), vaccine-induced thrombosis and thrombocytopenia (VITT), eczema, folliculitis decalvans, pseudofolliculitis barbae, leukoclastic vasculitis, hidradenitis suppurativa, palmar/plantar pustulosis, Lichenoid dermatitis, mycosis fungoides, sweet syndrome, follicular lymphoma, diffuse large B cell lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom 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, non-Hodgkin lymphoma, warm autoimmune hemolytic anemia (wAIHA), B-cell acute lymphoblastic leukemia (B-ALL), small lymphocytic lymphoma (SLL), intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, B-cell non-Hodgkin lymphoma, idiopathic thrombocytopenic purpura, IgG4-related diseases (IgG4-RD) and flares thereof, antiphospholipid syndrome (APS), membranous nephropathy (MN), immune thrombocytopenia, inflammatory bowel disease, itch associated with atopic dermatitis, lupus, cutaneous lupus, cutaneous lupus erythematosus, lupus nephritis, mixed connective tissue disease, multiple myeloma, multiple sclerosis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), sepsis, sepsis induced acute lung injury,

diffuse alveolar damage (DAD), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (SHIH), cytokine release syndrome (CRS), cutaneous form of systemic sclerosis (CREST), cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, urticaria, chronic spontaneous urticaria (CSU), chronic idiopathic urticaria (CIU), AI urticaria, and IgA nephropathy.

**[00383]** Embodiment 113. Use of the tablet of any one of Embodiments 1 to 110 for treating a disease involving mediation of the BTK receptor.

**[00384]** Embodiment 114. A tablet comprising: at least one compound chosen from (2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile (the compound of Formula (I)), and pharmaceutically acceptable salts thereof; at least one diluent present in an amount ranging from about 10% to about 50% by weight; at least one disintegrant present in an amount ranging from about 0.1% to about 15% by weight; at least one lubricant present in an amount ranging from about 0.01% to about 5% by weight; and optionally, at least one glidant.

**[00385]** Embodiment 115. The tablet of Embodiment 114, wherein the tablet comprises an intragranular phase and an extragranular phase.

**[00386]** Embodiment 116. The tablet of Embodiment 114 or 115, wherein: the at least one diluent is chosen from lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, calcium phosphate, hydroxypropylmethylcellulose, sucrose, calcium sulfate, calcium lactate, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, kaolin, sodium chloride, inositol, and bentonite; the at least one disintegrant is chosen from a starch, a cross-linked starch, a cellulose, a cross-linked cellulose, a cross-linked polymer, an alginate, a clay, a gum, a glycolate, bentonite, a natural sponge, a surfactant, a resin, citrus pulp, and sodium lauryl sulfate; the at least one lubricant is chosen from stearic acid, calcium hydroxide, talc, a hydrocarbon, a hydrogenated vegetable oil, higher fatty acids, a stearate, glycerol, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol, a methoxypolyethylene glycol, sodium oleate, sodium benzoate, glyceryl behenate, magnesium or sodium lauryl sulfate, colloidal silica, a starch, silicone oil, and a surfactant; and if present, the at least one glidant is chosen from colloidal silicon dioxide and talc.

**[00387]** Embodiment 117. The tablet of any one of Embodiments 114-116, wherein the at least one glidant is present in an amount greater than 0% to about 5% by weight.

**[00388]** Embodiment 118. The tablet of any one of Embodiments 114-117, wherein the compound of Formula (I) comprises an amorphous form.

[00389] Embodiment 119. The tablet of any one of Embodiments 114-117, wherein the compound of Formula (I) is present in at least 50% crystalline form, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, 99.5%, or 100% crystalline.

[00390] Embodiment 120. The tablet of any one of Embodiments 114-119, wherein the compound of Formula (I) is present in an amount ranging from about 200 mg to about 650 mg.

[00391] Embodiment 121. The tablet of Embodiment 120, wherein the compound of Formula (I) is present in an amount of about 400 mg.

[00392] Embodiment 122. The tablet of Embodiment 120, wherein the compound of Formula (I) is present in an amount of about 600 mg.

[00393] Embodiment 123. The tablet of any one of Embodiments 114-122, wherein the compound of Formula (I) is present in an amount of about 40% to about 75% by weight.

[00394] Embodiment 124. The tablet of Embodiment 123, wherein the compound of Formula (I) is present in the intragranular phase.

[00395] Embodiment 125. The tablet of any one of Embodiments 114-117, wherein the tablet comprises: about 45% to about 55% by weight amorphous compound of Formula (I), about 35% to about 40% by weight microcrystalline cellulose, about 5% to about 15% by weight crospovidone, and about 0.5% to about 5% by weight sodium stearyl fumarate, preferably wherein the compound of Formula (I) is present in an amount of about 400 mg.

[00396] Embodiment 126. The tablet of any one of Embodiments 114-117, wherein the tablet comprises: about 60% to about 70% by weight crystalline Form B of the compound of Formula (I), about 25% to about 35% by weight microcrystalline cellulose, about 0.5% to about 5% by weight crospovidone, about 0.1% to about 5% by weight magnesium stearate, and about 0.1% to about 5% by weight colloidal silicon dioxide, preferably wherein the compound of Formula (I) is present in an amount of about 600 mg.

[00397] Embodiment 127. The tablet of any one of Embodiments 114-126, further comprising a film-coating agent.

[00398] Embodiment 128. A method of treating a disease or condition mediated by BTK in a patient in need thereof, comprising administering to the patient the tablet of any one of Embodiments 114-127.

[00399] Embodiment 129. The method of Embodiment 128, wherein the disease or condition mediated by BTK is chosen from at least one of acne, allergy, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson syndrome, toxic epidermal necrolysis (TEN), pemphigus vulgaris, pemphigus foliaceus,

ankylosing spondylitis, antiphospholipid antibody syndrome, vasculitis, Guillain-Barre syndrome, scleroderma, Wegener's granulomatosis, psoriasis, granulomatosis with polyangiitis, thrombotic thrombocytopenic purpura, polyarteritis nodosa, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, asthma, moderate-to-severe asthma, mild asthma, moderate asthma, severe asthma, asthma that is not well controlled, autoimmune hepatitis, Behcet's disease, Grave's disease, nephritis, pancreatitis, primary biliary cirrhosis, ulcerative colitis, colitis, conjunctivitis, dermatitis, atopic dermatitis, drug eruptions, drug-induced thrombocytopenia (DITP), vaccine-induced thrombosis and thrombocytopenia (VITT), eczema, folliculitis decalvans, pseudofolliculitis barbae, leukoclastic vasculitis, hidradenitis suppurativa, palmar/plantar pustulosis, Lichenoid dermatitis, mycosis fungoides, sweet syndrome, follicular lymphoma, diffuse large B cell lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom 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, non-Hodgkin lymphoma, warm autoimmune hemolytic anemia (wAIHA), B-cell acute lymphoblastic leukemia (B-ALL), small lymphocytic lymphoma (SLL), intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, B-cell non-Hodgkin lymphoma, idiopathic thrombocytopenic purpura, IgG4-related diseases (IgG4-RD) and flares thereof, antiphospholipid syndrome (APS), membranous nephropathy (MN), immune thrombocytopenia, inflammatory bowel disease, itch associated with atopic dermatitis, lupus, cutaneous lupus, cutaneous lupus erythematosus, lupus nephritis, mixed connective tissue disease, multiple myeloma, multiple sclerosis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), sepsis, sepsis induced acute lung injury, diffuse alveolar damage (DAD), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (sHLH), cytokine release syndrome (CRS), cutaneous form of systemic sclerosis (CREST), cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, urticaria, chronic spontaneous urticaria (CSU), chronic idiopathic urticaria (CIU), AI urticaria, and IgA nephropathy.

**[00400]** Embodiment 130. Use of the tablet of any one of Embodiments 114-127 for treating a disease involving mediation of the BTK receptor.

## CLAIMS

1. A tablet comprising:
  - at least one compound chosen from (2-[(3R)-2-[4-amino-3-(2-fluoro-4-phenoxy-phenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidine-1-carbonyl]-4-methyl-4[4-(oxetan-3-yl)piperazin-1-yl]-pent-2-enenitrile (the compound of Formula (I)), and pharmaceutically acceptable salts thereof;
  - at least one diluent present in an amount ranging from about 10% to about 50% by weight;
  - at least one disintegrant present in an amount ranging from about 0.1% to about 15% by weight;
  - at least one lubricant present in an amount ranging from about 0.01% to about 5% by weight; and optionally, at least one glidant.
2. The tablet of claim 1, wherein the tablet comprises an intragranular phase and an extragranular phase.
3. The tablet of claim 1 or claim 2, wherein:
  - the at least one diluent is chosen from lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, calcium phosphate, hydroxypropylmethylcellulose, sucrose, calcium sulfate, calcium lactate, hydrolyzed cereal solids, amylose, powdered cellulose, calcium carbonate, glycine, kaolin, sodium chloride, inositol, and bentonite;
  - the at least one disintegrant is chosen from a starch, a cross-linked starch, a cellulose, a cross-linked cellulose, a cross-linked polymer, an alginate, a clay, a gum, a glycolate, bentonite, a natural sponge, a surfactant, a resin, citrus pulp, and sodium lauryl sulfate;
  - the at least one lubricant is chosen from stearic acid, calcium hydroxide, talc, a hydrocarbon, a hydrogenated vegetable oil, higher fatty acids, a stearate, glycerol, talc, waxes, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol, a methoxypolyethylene glycol, sodium oleate, sodium benzoate, glyceryl behenate, magnesium or sodium lauryl sulfate, colloidal silica, a starch, silicone oil, and a surfactant; and
  - if present, the at least one glidant is chosen from colloidal silicon dioxide and talc.
4. The tablet of any one of the preceding claims, wherein the at least one glidant is present in an amount greater than 0% to about 5% by weight.

5. The tablet of any one of the preceding claims, wherein the compound of Formula (I) comprises an amorphous form.
6. The tablet of any one of claims 1 to 4, wherein the compound of Formula (I) is present in at least 50% crystalline form, such as at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, 99.5%, or 100% crystalline.
7. The tablet of any one of the preceding claims, wherein the compound of Formula (I) is present in an amount ranging from about 200 mg to about 650 mg.
8. The tablet of claim 7, wherein the compound of Formula (I) is present in an amount of about 400 mg.
9. The tablet of claim 7, wherein the compound of Formula (I) is present in an amount of about 600 mg.
10. The tablet of any one of the preceding claims, wherein the compound of Formula (I) is present in an amount of about 40% to about 75% by weight.
11. The tablet of claim 10, wherein the compound of Formula (I) is present in the intragranular phase.
12. The tablet of any one of claims 1 to 4, wherein the tablet comprises:  
about 45% to about 55% by weight amorphous compound of Formula (I),  
about 35% to about 40% by weight microcrystalline cellulose,  
about 5% to about 15% by weight crospovidone, and  
about 0.5% to about 5% by weight sodium stearyl fumarate,  
preferably wherein the compound of Formula (I) is present in an amount of about 400 mg.
13. The tablet of any one of claims 1 to 4, wherein the tablet comprises:  
about 60% to about 70% by weight crystalline Form B of the compound of Formula (I),  
about 25% to about 35% by weight microcrystalline cellulose,

about 0.5% to about 5% by weight crospovidone,  
about 0.1% to about 5% by weight magnesium stearate, and  
about 0.1% to about 5% by weight colloidal silicon dioxide,  
preferably wherein the compound of Formula (I) is present in an amount of about 600 mg.

14. The tablet of any one of the preceding claims, further comprising a film-coating agent.

15. A method of treating a disease or condition mediated by BTK in a patient in need thereof, comprising administering to the patient the tablet of any one of claims 1 to 14.

16. The method of claim 15, wherein the disease or condition mediated by BTK is chosen from at least one of acne, allergy, alopecia areata, vitiligo, pyoderma gangrenosum, membrane pemphigoid, epidermolysis bullosa acquisita, Steven Johnson syndrome, toxic epidermal necrolysis (TEN), pemphigus vulgaris, pemphigus foliaceus, ankylosing spondylitis, antiphospholipid antibody syndrome, vasculitis, Guillain-Barre syndrome, scleroderma, Wegener's granulomatosis, psoriasis, granulomatosis with polyangiitis, thrombotic thrombocytopenic purpura, polyarteritis nodosa, arthritis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, asthma, moderate-to-severe asthma, mild asthma, moderate asthma, severe asthma, asthma that is not well controlled, autoimmune hepatitis, Behcet's disease, Grave's disease, nephritis, pancreatitis, primary biliary cirrhosis, ulcerative colitis, colitis, conjunctivitis, dermatitis, atopic dermatitis, drug eruptions, drug-induced thrombocytopenia (DITP), vaccine-induced thrombosis and thrombocytopenia (VITT), eczema, folliculitis decalvans, pseudofolliculitis barbae, leucoclastic vasculitis, hidradenitis suppurativa, palmar plantar pustulosis, Lichenoid dermatitis, mycosis fungoides, sweet syndrome, follicular lymphoma, diffuse large B cell lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom 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, non-Hodgkin lymphoma, warm autoimmune hemolytic anemia (wAIHA), B-cell acute lymphoblastic leukemia (B-ALL), small lymphocytic lymphoma (SLL), intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, lymphomatoid granulomatosis, B-cell non-Hodgkin lymphoma, idiopathic thrombocytopenic purpura, IgG4-related diseases (IgG4-RD) and flares

thereof, antiphospholipid syndrome (APS), membranous nephropathy (MN), immune thrombocytopenia, inflammatory bowel disease, itch associated with atopic dermatitis, lupus, cutaneous lupus, cutaneous lupus erythematosus, lupus nephritis, mixed connective tissue disease, multiple myeloma, multiple sclerosis, systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), sepsis, sepsis induced acute lung injury, diffuse alveolar damage (DAD), macrophage activation syndrome (MAS), secondary hemophagocytic lymphohistiocytosis (sHLH), cytokine release syndrome (CRS), cutaneous form of systemic sclerosis (CREST), cryoglobulinemia, primary biliary sclerosis, sclerosing cholangitis, urticaria, chronic spontaneous urticaria (CSU), chronic idiopathic urticaria (CIU), AI urticaria, and IgA nephropathy.

17. Use of the tablet of any one of claims 1 to 14 for treating a disease involving mediation of the BTK receptor.