

Crystalline Forms of a PI3K Inhibitor and Uses of Same**RELATED APPLICATIONS**

This application claims the benefit of priority to U.S. Provisional Appl. No. 63/532,700,  
5 filed on August 15, 2023, which is hereby incorporated by reference in its entirety including any  
drawings.

**SEQUENCE LISTING**

This application contains a Sequence Listing that has been submitted electronically  
10 as an XML file named "50006-0100WO1\_ST26\_SL.XML." The XML file, created on August  
12, 2024, is 2,961 bytes in size. The material in the XML file is hereby incorporated by reference  
in its entirety.

**FIELD**

15 Disclosed herein are crystalline forms of phosphatidylinositol 4,5-bisphosphate 3-kinase  
(PI3K) isoform alpha (PI3K $\alpha$ ) inhibitors.

**BACKGROUND**

1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-  
20 trifluoroethyl)urea is a phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) isoform alpha  
(PI3K $\alpha$ ) inhibitor disclosed in WO 2022/265993, which is incorporated by reference herein in its  
entirety. PI3K $\alpha$  is encoded by the *PIK3CA* gene is a part of the PI3K/AKT/TOR signaling network  
and is altered in several human cancers. Several investigators have demonstrated the role of  
PI3K/AKT signaling is involved in physiological and pathophysiological functions that drive  
25 tumor progression such as metabolism, cell growth, proliferation, angiogenesis and metastasis.  
(*See*, Fruman, D.A. Cell 2017, 170, 605–635 and Janku, F. et al., Nat. Rev. Clin. Oncol. 2018, 15,  
273–291.) Suppression (e.g., pharmacological or genetic) of PI3K/AKT/TOR signaling may cause  
cancer cell death and regression of tumor growth.

Polymorphism, the occurrence of different crystalline forms, is a property of some  
30 molecules and molecular complexes. A given compound may give rise to a variety of polymorphs  
having distinct crystal structures and physical properties such as melting point, thermal behaviors,

X-ray diffraction pattern, IR spectrum, and solid state  $^{13}\text{C}$  NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

Different salts and crystalline forms (including solvated forms) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and crystalline forms and solvates may provide a basis for improving formulation and/or clinical properties. Different salts and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms.

### SUMMARY

Some embodiments provide a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

Some embodiments provide a pharmaceutical composition comprising a crystalline form disclosed herein and a pharmaceutically acceptable carrier.

Some embodiments provide a method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the crystalline form disclosed herein, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition comprising a crystalline form disclosed herein and a pharmaceutically acceptable carrier.

Some embodiments provide a method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of a *PIK3CA* gene, a  $\text{PI3K}\alpha$  protein, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of the crystalline form disclosed herein, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition comprising a crystalline form disclosed herein and a pharmaceutically acceptable carrier.

Some embodiments provide a method of treating a  $\text{PI3K}\alpha$ -associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a  $\text{PI3K}\alpha$ -associated cancer a therapeutically effective amount of the crystalline form disclosed herein, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition comprising a crystalline form disclosed herein and a pharmaceutically acceptable carrier.

Some embodiments provide a method for modulating  $\text{PI3K}\alpha$  in a mammalian cell, the



method comprising contacting the mammalian cell with an effective amount of the crystalline form disclosed herein, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition comprising a crystalline form disclosed herein and a pharmaceutically acceptable carrier.

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#### Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

15 The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to  $\pm 10\%$  of the stated number or numerical range.

The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

The term “inhibit” or “inhibition of” means to reduce by a measurable amount, or to prevent entirely (e.g., 100% inhibition).

25 The terms “polymorph” and “polymorphic form” are used interchangeably and refer to different crystalline forms of a single compound. That is, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct solid state physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct solid state physical properties, such as different solubility profiles, dissolution rates, melting point temperatures, flowability, and/or different X-ray diffraction peaks.

30 The term “amorphous” means a solid in a non-crystalline state. Amorphous solids are disordered arrangements of molecules and therefore possess no distinguishable crystal lattice or

unit cell and consequently have no definable long range ordering. Solid state forms can be determined by polarized light microscopy, X-ray powder diffraction ("XRPD"), differential scanning calorimetry ("DSC"), or other standard techniques known to those of skill in the art.

As used herein, a compound is "substantially pure" if the compound contains an insignificant amount of other components. Such components can include, for example, starting materials, residual solvents, other polymorphic or crystalline forms, the opposite enantiomer, other salt forms, other solvates, or any other impurities that can result from the preparation, isolation, and/or recrystallization of the compounds provided herein. In some embodiments, the other components can include, for example, starting materials, residual solvents, other polymorphic or crystalline forms, the opposite enantiomer, other salt forms, or any other impurities that can result from the preparation, isolation, and/or recrystallization of the compounds provided herein. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is "substantially pure" if the crystalline form consists of at least about 95% by weight of the crystalline form. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is "substantially pure" if the crystalline form constitutes at least about 97%, about 98%, about 99%, or about 99.5% by weight of the crystalline form.

The phrase "therapeutically effective amount" means an amount of compound that, when administered to a subject in need of such treatment, is sufficient to (i) treat a PI3K $\alpha$  protein-associated disease or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The term "pharmaceutical composition" as used herein is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present disclosure encompass any composition made by admixing a compound of the present disclosure, or a pharmaceutically acceptable salt and/or solvate thereof, and a pharmaceutically acceptable carrier.

The term “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, e.g., *Remington: The Science and Practice of Pharmacy*, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 6th ed.; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salts not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids

such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

5 The term “pharmaceutically acceptable solvate” refers to a solvate of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. A solvate is a crystalline solid that contains molecules of solvent inside its crystal lattice. Solvate forms of a compound can, in some instances, favorably alter the properties of the compound, such as solubility, stability, dissolution rate, and mechanical behavior. An exemplary solvate is a hydrate, which is a water solvate. When the  
10 average number of water molecules present in each repeating unit (i.e., unit cell) of the crystal lattice of a hydrate is known, the hydrate is affixed with a prefix denoting the average number of water molecules in each unit cell. For example, a monohydrate contains an average of one water molecule per unit cell, a dihydrate contains an average of two water molecules per unit cell, and a hemihydrate contains an average of half of a water molecule per unit cell. For more information,  
15 see, e.g., K.R. Morris, *Polymorphism in Pharmaceutical Solids* 1999, pages 125-181; Jeffrey, G.A. *Acc. Chem. Res.* 1969, 344-352; *Rev. Pure Appl. Chem.*, 1963, 50-90; *Encyclopedia of Pharmaceutical Technology*, 1993, 7, pages 393-441, each of which is incorporated herein in its entirety.

The term “pharmaceutical composition” refers to a mixture of a compound described  
20 herein with other chemical components (referred to collectively herein as “pharmaceutically acceptable excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary,  
25 and topical administration.

As used herein, the term “subject” refers to any animal, including mammals such as primates (e.g., humans), mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the subject is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be  
30 treated and/or prevented.

As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The details of one or more embodiments of this disclosure are set forth in the accompanying drawings and the description below. Other features and advantages of the present disclosure will be apparent from the description and drawings, and from the claims.

### DESCRIPTION OF DRAWINGS

FIG. 1 Depicts Polarized Light Microscopy (PLM) images of Compound A solids prior to crystallization experiments.

FIG. 2. Depicts the XRPD diffractogram of Compound A solids prior to crystallization experiments, assigned as Form 1\*.

FIG. 3. Depicts the Thermogravimetric Analysis/ Differential Scanning Calorimetry (TGA/DSC) thermogram of Compound A solids prior to crystallization experiments, assigned as Form 1\*.

FIG. 4 Depicts the XRPD diffractogram of Compound A, hemi-hydrate Form 1 prepared by the procedure in Example 10.

FIG. 5 Depicts the XRPD diffractogram of Compound A, Form 1\*.

FIG. 6 Depicts the XRPD diffractogram of Compound A, Form 2.

FIG. 7 Depicts the XRPD diffractogram of Compound A, Form 3.

FIG. 8 Depicts the XRPD diffractogram of Compound A, Form 4.

FIG. 9 Depicts Polarized Light Microscopy (PLM) images of Form 1 obtained from the crystallization process of Example 9, after drying and equilibration under ambient conditions (see Example 12).

FIG. 10 Depicts the Infrared (IR) spectrum of Form 1 obtained from the crystallization process of Example 9, after drying and equilibration under ambient conditions (see Example 12).

FIG. 11 Depicts the  $^1\text{H}$ -NMR spectrum of Form 1 obtained from the crystallization process of Example 9, after drying and equilibration under ambient conditions (see Example 12).

FIG. 12 Depicts the  $^{19}\text{F}$ -NMR spectrum of Form 1 obtained from the crystallization process of Example 9, after drying and equilibration under ambient conditions (see Example 12).

5 FIG. 13 Depicts XRPD diffractograms of Compound A mesylate salt formed in Example 2, Procedure A: (A) subsample of mesylate salt taken during crystallization, (B) wet mesylate salt, (C) mesylate salt after drying, (D) wet mesylate salt reference, and (E) dry mesylate salt reference.

FIG. 14 Depicts TG/DSC thermogram of Compound A mesylate salt formed in Example 2, Procedure A.

10 FIG. 15 Depicts XRPD diffractograms of Compound A mesylate salt suspended in different pH buffers for 1 h in disproportion studies (Example 2, Procedure B).

FIG. 16 Depicts the XRPD diffractogram of amorphous (lyophilized) Compound A used as input for the primary polymorph screen (Example 5) and other crystallization experiments along with the XRPD of Form 1\* as a reference.

15 FIG. 17 Depicts the XRPD diffractograms of Compound A crystalline forms obtained in the primary polymorph screen (Example 5): 1-Butanol (Form 1\*), 1-Propanol:water 50:50 (Form 1), and 2-Propanol: water 80:20 (Form 1).

FIG. 18 Depicts the XRPD diffractograms of Compound A crystalline forms obtained in the primary polymorph screen (Example 5): isopropyl acetate:heptane 70:30 (Form 3), isopropyl acetate:heptane:acetonitrile:water 68:30:1:1 (Form 3), methanol:water 80:20 (Form 1); methyl isopropyl ketone (Form 3), and tetrahydrofuran THF (Form 3).

FIG. 19 Depicts the XRPD diffractograms of Compound A Form 1 obtained from MeOH/water in the preliminary crystallization experiments (Example 8) before and after grinding along with the XRPD of a known impurity (Impurity 1) in Compound A.

25 FIG. 20 Depicts the XRPD diffractograms of Compound A Form 1 obtained from EtOH/water in the preliminary crystallization experiments (Example 8) before and after grinding along with the XRPD of a known impurity (Impurity 1) in Compound A.

FIG. 21 Depicts the XRPD diffractograms of Compound A wet Form 1 (prior to drying) obtained during the crystallization process optimization in Example 9, Protocol A before and after grinding along with the XRPD of a known impurity (Impurity 1) in Compound A.

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FIG. 22 Depicts the XRPD diffractograms of Compound A Form 1 obtained during the crystallization process optimization in Example 9, Protocol B before and after grinding along with the XRPD of a known impurity (Impurity 1) in Compound A.

FIG. 23 Depicts the XRPD diffractograms of Compound A Form 1 wet and dried solid obtained during the crystallization process optimization in Example 9, Protocol C before and after grinding along with the XRPD of a known impurity (Impurity 1) in Compound A.

FIG. 24 Depicts the XRPD diffractograms of Compound A wet Form 1 (prior to drying) obtained during the crystallization process optimization in Example 9, Protocol D before and after grinding along with the XRPD of a known impurity (Impurity 1) in Compound A.

FIG. 25 Depicts the XRPD diffractograms of Compound A solids in competitive slurry experiments (Example 11): Top frames show Form 1\* and Form 1 references; (A) 2-propanol:water 20:80 4 days at 50°C shows Form 1 and trace of Form1\*; (B) 2-propanol:water 20:80 10 days at 50°C shows Form 1 only.

FIG. 26 Depicts the XRPD diffractograms of Compound A solids in competitive slurry experiments (Example 11): Top frames show Form 1\* and Form 1 references; (A) Solids obtained from 2-propanol:water 20:80 after 4 days at 20°C shows Form 1 and trace of Form1\*, (B) solids obtained from 2-propanol:water 20:80 10 days at 20°C shows Form 1 with trace of Form 1\*.

FIG. 27 Depicts the XRPD diffractograms of Compound A solids in the stability study (Example 12): Top frames show Form 1 reference and over-dried solid (Form 4); bottom two frames show that Compound A over-dried solid (Form 4) reverts back to Form 1 when exposed to ambient conditions and 60% relative humidity.

FIG. 28 Depicts the TG/DSC thermogram of solids (confirmed to be Form 1 by XRPD, see FIG 27) obtained after equilibration protocols (Example 12).

FIG. 29 Depicts the DSC thermogram (first heat cycle) of solids (confirmed to be Form 1 by XRPD, see FIG 27) obtained after equilibration protocols (Example 12).

FIG. 30 Depicts the DSC thermogram (first cool cycle) of solids (confirmed to be Form 1 by XRPD, see FIG 27) obtained after equilibration protocols (Example 12).

FIG. 31 Depicts the DSC thermogram (second heat cycle) of solids (confirmed to be Form 1 by XRPD, see FIG 27) obtained after equilibration protocols (Example 12).

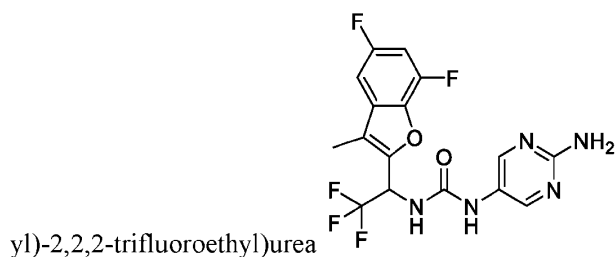
FIG. 32 Depicts the dynamic vapor sorption (DVS) plots of solids (confirmed to be Form 1 by XRPD, see FIG 27) obtained after equilibration protocols (Example 12); (A) kinetic plot; (B) isotherm plot.

FIG. 33 Depicts the XRPD diffractograms of solids (confirmed to be Form 1 by XRPD, see FIG 27) obtained after equilibration protocols (Example 12) after milling from 90 to 540 seconds.

FIG. 34 Depicts the TG/DSC thermogram of solids (confirmed to be Form 3 by XRPD) obtained from polymorph screen (Example 5, Procedure A) from isopropyl acetate:heptane:acetonitrile:water 68:30:1:1 % v/v/v/v.

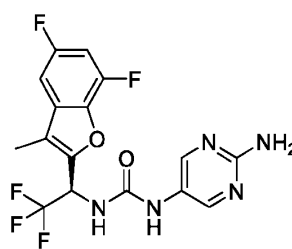
### DETAILED DESCRIPTION

Described herein is 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-



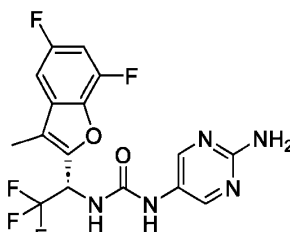
Described herein is (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-

methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (also referred to as "Compound A").





Described herein is (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-



methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea

Described herein are crystalline forms of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

5 In some embodiments, the crystalline forms of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea are crystalline forms of racemic, non-racemic (i.e., scalemic), (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the crystalline forms of  
10 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea are crystalline forms of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the crystalline forms of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea are crystalline forms of  
15 (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the crystalline forms of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea are crystalline forms of racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the crystalline forms of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea are crystalline forms of scalemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.  
20

Also provided herein is amorphous (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the amorphous (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is  
25 characterized by the XRPD pattern that is substantially the same as that shown in FIG. 16.

These crystalline forms are useful, e.g., for treating a condition, disease or disorder in which increased (e.g., excessive) PI3K $\alpha$  activation contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder (e.g., cancer) in a subject (e.g., a human). This disclosure also provides compositions containing the same as well as methods of using and making the same.

Some embodiments provide a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (also referred to herein as "Compound A"), or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a pharmaceutically acceptable solvate. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hydrate. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hemihydrate.

Some embodiments provide a crystalline form of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a pharmaceutically acceptable solvate. In some embodiments, the (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hydrate. In some embodiments, the (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hemi-hydrate.

Some embodiments provide a crystalline form of racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a pharmaceutically acceptable solvate. In some embodiments, the racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hydrate. In some embodiments, the racemic 1-(2-aminopyrimidin-5-yl)-

3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hemi-hydrate.

Some embodiments provide a crystalline form of non-racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the non-racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a pharmaceutically acceptable solvate. In some embodiments, the non-racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hydrate. In some embodiments, the non-racemic 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a hemi-hydrate.

The skilled artisan will recognize that the relative intensities of X-ray powder diffraction pattern peaks can vary depending on the sample preparation technique, crystal size distribution, various filters used, sample mounting procedure, and the particular instrument employed. Accordingly, depending on the type of the instrument and settings employed (including filters), new peaks may be observed in subsequently obtained patterns; or peaks observed in previously obtained patterns may have a negligible relative intensities (and hence may not be observed) in subsequently obtained patterns. As such, the absence of one or more of the lower relative intensity peaks described above may not, in and of itself, establish that a particular polymorphic form (e.g., Form 1, Form 1\*, Form 2, Form 3, or Form 4) is not present (e.g., in a sample). However, the presence of the lower relative intensity peaks described above can, in general, be used to further establish the presence of a particular polymorphic form (e.g., Form 1, Form 1\*, Form 2, Form 3, or Form 4) in a sample.

#### *Form 1*

In some embodiments, the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $18.3 \pm 0.2$  degrees  $2\theta$ . For ease of exposition, the aforementioned form is referred to herein as "Form 1." The X-ray powder diffraction pattern of Form 1 can also include one or more additional characteristic peaks.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $6.4 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $6.4 \pm 0.2$  degrees  $2\theta$  has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $15.8 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $15.8 \pm 0.2$  degrees  $2\theta$  has the second relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $18.3 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $18.3 \pm 0.2$  degrees  $2\theta$  has the third highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 1 has a peak at  $22.3 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $22.3 \pm 0.2$  degrees  $2\theta$  has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $20.8 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $20.8 \pm 0.2$  degrees  $2\theta$  has the fifth highest relative intensity.

10 In some embodiments, the XRPD pattern of Form 1 has a peak at  $19.3 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $19.3 \pm 0.2$  degrees  $2\theta$  has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $24.0 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $24.0 \pm 0.2$  degrees  $2\theta$  has the seventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $26.9 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $26.9 \pm 0.2$  degrees  $2\theta$  has the eighth highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 1 has a peak at  $14.6 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $14.6 \pm 0.2$  degrees  $2\theta$  has the ninth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $31.3 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $31.3 \pm 0.2$  degrees  $2\theta$  has the tenth highest relative intensity.

20 In some embodiments, the XRPD pattern of Form 1 has a peak at  $28.3 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $28.3 \pm 0.2$  degrees  $2\theta$  has the eleventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $29.2 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $29.2 \pm 0.2$  degrees  $2\theta$  has the twelfth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $22.8 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $22.8 \pm 0.2$  degrees  $2\theta$  has the thirteenth highest relative intensity.

25 In some embodiments, the XRPD pattern of Form 1 has a peak at  $28.0 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $28.0 \pm 0.2$  degrees  $2\theta$  has the fourteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $25.3 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $25.3 \pm 0.2$  degrees  $2\theta$  has the fifteenth highest relative intensity.

30 In some embodiments, the XRPD pattern of Form 1 has a peak at  $21.5 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $21.5 \pm 0.2$  degrees  $2\theta$  has the sixteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $19.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $19.9 \pm 0.2$  degrees  $2\theta$  has the seventeenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $27.6 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $27.6 \pm 0.2$  degrees  $2\theta$  has the eighteenth highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 1 has a peak at  $20.5 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.5 \pm 0.2$  degrees  $2\theta$  has the nineteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $21.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $21.8 \pm 0.2$  degrees  $2\theta$  has the twentieth highest relative intensity.

10 In some embodiments, the XRPD pattern of Form 1 has a peak at  $25.1 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $25.1 \pm 0.2$  degrees  $2\theta$  has the twenty-first highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $25.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $25.8 \pm 0.2$  degrees  $2\theta$  has the twenty-second highest relative intensity.

15 In some embodiments, the crystalline form is Form 1, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 15.8, and 18.3.

In some embodiments, the crystalline form is Form 1, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 14.6, 15.8, 18.3, 19.3, 20.8, 22.3, 24.0, 26.9, 28.3, 29.2 and 31.3.

20 In some embodiments, the crystalline form is Form 1, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 15.8, 18.3, 22.3, 20.8, 19.3, 24.0, 26.9, 14.6, 31.3, 28.3, 29.2, 22.8, 28.0, 25.3, 21.5, 19.9, 27.6, 20.5, 21.8, 25.1, and 25.8.

In some embodiments, the crystalline form is Form 1, characterized by an XRPD pattern substantially the same as that shown in FIG. 4.

25 In some embodiments, the crystalline form is Form 1 having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 0.5% to about 5% (e.g., about 1% to about 3%, about 2% to about 3%, or about 2.3%) at about 70 °C to about 140 °C (e.g., about 90 °C to about 130 °C, about 90 °C to about 120 °C, about 90 °C to about 115 °C, about 100 °C to about 140 °C, about 110 °C to about 140 °C, about 100 °C to about 120 °C, about 105 °C to about 120 °C, about 109 °C to about 115 °C, about 75 °C to about 125 °C, about 85 °C to about 113 °C, about 85 °C to about 105 °C, or about 112 °C. In some embodiments, the crystalline form is Form 1  
30 having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.3% at about 112.5 °C. In some embodiments, the crystalline form is Form 1 having a thermogravimetric

analysis (TGA) curve characterized by a weight loss of about 2.3% at about 85 °C to about 113 °C.

In some embodiments, the crystalline form is Form 1 having a TGA curve characterized by a weight loss of about 5% to about 30% (e.g., about 5% to about 27%, about 5% to about 25%, about 5% to about 22%, about 10% to about 25%, about 20% to about 22%, about 14% to about 20%, or about 17.6%) at about 150 °C to about 250 °C (e.g., about 230 to about 260 °C about 230 °C to about 250 °C, about 162 °C to about 248 °C, about 230 °C to about 240 °C, about 240 °C to about 260 °C, about 240 °C to about 250 °C, about 242 °C to about 248 °C, or about 245 °C). In some embodiments, the crystalline form is Form 1 having a TGA curve characterized by a weight loss of about 17.6% at about 245 °C. In some embodiments, the crystalline form is Form 1 having a TGA curve characterized by a weight loss of about 17.6% at about 162 °C to about 248 °C.

In some embodiments, the crystalline form is Form 1 having a TGA curve that is substantially the same as that shown in FIG. 28. In some embodiments, the crystalline form is Form 1 having a Thermal Gravimetric/Differential Scanning Calorimetry (TG/DSC) thermogram that is substantially the same as that shown in FIG. 28.

In some embodiments, the crystalline form is Form 1 having a differential scanning calorimetry (DSC) first heat cycle thermogram having an endothermic event having an onset temperature of about 105 °C and a peak of about 129 °C, an endothermic event having an onset temperature of about 158 °C and a peak of about 162 °C and an endothermic event having an onset temperature of about 174 °C and a peak of about 177 °C.

In some embodiments, the crystalline form is Form 1 having a Differential Scanning Calorimetry (DSC) thermogram that is substantially the same as that shown in FIG. 29.

In some embodiments, the crystalline form is Form 1 having a DSC curve that is substantially the same as that shown in FIG. 29.

In some embodiments, the crystalline form is Form 1 having a DSC first cooling cycle thermogram characterized by a single exothermic event at with an onset temperature of 151 °C and a peak temperature of 147 °C.

In some embodiments, the crystalline form is Form 1 having a DSC first cooling cycle thermogram substantially the same as that shown in FIG. 30.

In some embodiments, the Form 1 is a hemi-hydrate.

In some embodiments, the enantiomeric excess (ee) of crystalline Form 1 is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%).

In some embodiments, the Form 1 is substantially pure.

5 *Form 1\**

In some embodiments, the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $6.3 \pm 0.2$  degrees  $2\theta$ . For ease of exposition, the aforementioned form is referred to herein as "Form 1\*." The X-ray powder diffraction pattern of Form 1\* can also include one or more additional characteristic peaks.

10 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $6.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $6.3 \pm 0.2$  degrees  $2\theta$  has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $15.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.8 \pm 0.2$  degrees  $2\theta$  has the second highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $20.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.8 \pm 0.2$  degrees  $2\theta$  has the third highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $15.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.9 \pm 0.2$  degrees  $2\theta$  has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $19.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $19.8 \pm 0.2$  degrees  $2\theta$  has the fifth highest relative intensity.

20 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $19.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $19.3 \pm 0.2$  degrees  $2\theta$  has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $28.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $28.0 \pm 0.2$  degrees  $2\theta$  has the seventh highest relative intensity.

25 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $27.6 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $27.6 \pm 0.2$  degrees  $2\theta$  has the eighth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $24.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $24.0 \pm 0.2$  degrees  $2\theta$  has the ninth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $22.1 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $22.1 \pm 0.2$  degrees  $2\theta$  has the tenth highest relative intensity.

30 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $29.2 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $29.2 \pm 0.2$  degrees  $2\theta$  has the eleventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $26.4 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $26.4 \pm 0.2$  degrees  $2\theta$  has the twelfth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $21.6 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $21.6 \pm 0.2$  degrees  $2\theta$  has the thirteenth highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $14.4 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $14.4 \pm 0.2$  degrees  $2\theta$  has the fourteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $14.5 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $14.5 \pm 0.2$  degrees  $2\theta$  has the fifteenth highest relative intensity.

10 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $26.1 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $26.1 \pm 0.2$  degrees  $2\theta$  has the sixteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $28.6 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $28.6 \pm 0.2$  degrees  $2\theta$  has the seventeenth highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 1\* has a peak at  $20.3 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $20.3 \pm 0.2$  degrees  $2\theta$  has the eighteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $31.2 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $31.2 \pm 0.2$  degrees  $2\theta$  has the nineteenth highest relative  
20 intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $26.8 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $26.8 \pm 0.2$  degrees  $2\theta$  has the twentieth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $18.9 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $18.9 \pm 0.2$  degrees  $2\theta$  has the twenty-first highest relative  
25 intensity.

In some embodiments, the XRPD pattern of Form 1\* has a peak at  $31.5 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $31.5 \pm 0.2$  degrees  $2\theta$  has the twenty-second highest relative  
intensity.

In some embodiments, the crystalline form is Form 1\*, and wherein the XRPD pattern has  
30 peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 15.8, and 20.8.



In some embodiments, the crystalline form is Form 1\*, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 15.8, 20.8, 15.9, 19.8, 19.3, 28.0, 27.6, 24.0, and 22.1.

In some embodiments, the crystalline form is Form 1\*, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 15.8, 20.8, 15.9, 19.8, 19.3, 28.0, 27.6, 24.0, 22.1, 29.2, 26.4, 21.6,  
5 14.4, 14.5, 26.1, 28.6, 20.3, 31.2, 26.8, 18.9, and 31.5.

In some embodiments, the crystalline form is Form 1\*, characterized by an XRPD pattern substantially the same as that shown in FIG. 2.

In some embodiments, the crystalline form is Form 1\* having a TG/DSC thermogram characterized by multiple weight loss events prior to degradation, with an about 2.5 % weight loss  
10 between about 72 °C and about 114 °C (theoretically equivalent to 0.5 moles of water), an about 2.2 % weight loss between about 147 °C and about 185 °C (theoretically equivalent to 0.5 moles of water) and an about 12.2 % weight loss between about 185 °C and about 252 °C.

In some embodiments, the crystalline form is Form 1\* having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 0.5% to about 5% (e.g., about 1% to about  
15 3%, about 2% to about 3%, or about 2.5%) at about 60 °C to about 140 °C (e.g., about 65 °C to about 125 °C, at about 70 °C to about 120 °C, or about 72 °C to about 114 °C. In some embodiments, the crystalline form is Form 1\* having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.5% at about 72 °C and 114 °C.

In some embodiments, the crystalline form is Form 1\* having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 0.5% to about 5% (e.g., about 1% to about  
20 23%, about 10% to about 15%, about 12% to about 13%, or about 12.2%) at about 165 °C to about 275 °C (e.g., about 175 °C to about 265 °C, at about 180 °C to about 260 °C, or about 185 °C to about 252 °C). In some embodiments, the crystalline form is Form 1\* having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 12.2% at about 185 °C to about 252  
25 °C.

In some embodiments, the crystalline form is Form 1\* having a TGA curve that is substantially the same as that shown in FIG. 3. In some embodiments, the crystalline form is Form 1\* having a Thermal Gravimetric/Differential Scanning Calorimetry (TG/DSC) thermogram that  
is substantially the same as that shown in FIG. 3.

In some embodiments, the crystalline form is Form 1\* having a TG/DSC thermogram characterized by an endothermic event having an onset temperature of about 86 °C and a peak at  
30

about 102 °C, an endothermic event having an onset temperature of about 154 °C and a peak at about 158 °C, and an endothermic event having an onset temperature of about 172 °C and a peak at about 176 °C. In some embodiments, the TG/DSC thermogram curve is characterized by an endothermic event having an onset temperature of about 294 °C (peak at about 301 °C) that is, in some embodiments, associated with degradation.

In some embodiments, the crystalline form is Form 1\* having a Differential Scanning Calorimetry (DSC) thermogram that is substantially the same as that shown in FIG. 3.

In some embodiments, the Form 1\* is a hemi-hydrate.

In some embodiments, the enantiomeric excess (ee) of Form 1\* is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%.

In some embodiments, the Form 1\* is substantially pure.

#### *Form 2*

In some embodiments, the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $6.2 \pm 0.2$  degrees  $2\theta$ . For ease of exposition, the aforementioned form is referred to herein as "Form 2." The X-ray powder diffraction pattern of Form 2 can also include one or more additional characteristic peaks.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $6.2 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $6.2 \pm 0.2$  degrees  $2\theta$  has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $15.2 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.2 \pm 0.2$  degrees  $2\theta$  has the second highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $15.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.3 \pm 0.2$  degrees  $2\theta$  has the third highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $20.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.9 \pm 0.2$  degrees  $2\theta$  has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $21.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $21.9 \pm 0.2$  degrees  $2\theta$  has the fifth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $22.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $22.0 \pm 0.2$  degrees  $2\theta$  has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $21.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $21.0 \pm 0.2$  degrees  $2\theta$  has the seventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $18.7 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $18.7 \pm 0.2$  degrees  $2\theta$  has the eighth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $18.7 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $18.7 \pm 0.2$  degrees  $2\theta$  has the ninth highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 2 has a peak at  $26.9 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $26.9 \pm 0.2$  degrees  $2\theta$  has the tenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $24.0 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $24.0 \pm 0.2$  degrees  $2\theta$  has the eleventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $21.1 \pm 0.2$  degrees  $2\theta$ .  
10 In some embodiments, the peak at  $21.1 \pm 0.2$  degrees  $2\theta$  has the twelfth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $27.4 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $27.4 \pm 0.2$  degrees  $2\theta$  has the thirteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $28.0 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $28.0 \pm 0.2$  degrees  $2\theta$  has the fourteenth highest relative  
15 intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $14.7 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $14.7 \pm 0.2$  degrees  $2\theta$  has the fifteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $20.6 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $20.6 \pm 0.2$  degrees  $2\theta$  has the sixteenth highest relative intensity.

20 In some embodiments, the XRPD pattern of Form 2 has a peak at  $19.9 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $19.9 \pm 0.2$  degrees  $2\theta$  has the seventeenth highest relative  
intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $19.4 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $19.4 \pm 0.2$  degrees  $2\theta$  has the eighteenth highest relative  
25 intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $21.5 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $21.5 \pm 0.2$  degrees  $2\theta$  has the nineteenth highest relative  
intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $17.7 \pm 0.2$  degrees  $2\theta$ .  
30 In some embodiments, the peak at  $17.7 \pm 0.2$  degrees  $2\theta$  has the twentieth highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $26.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $26.0 \pm 0.2$  degrees  $2\theta$  has the twenty-first highest relative intensity.

In some embodiments, the XRPD pattern of Form 2 has a peak at  $28.3 \pm 0.2$  degrees  $2\theta$ .  
5 In some embodiments, the peak at  $28.3 \pm 0.2$  degrees  $2\theta$  has the twenty-second highest relative intensity.

In some embodiments, the crystalline form is Form 2, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.2, 15.2, and 15.3.

In some embodiments, the crystalline form is Form 2, and wherein the XRPD pattern has  
10 peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.2, 15.2, 15.3, 20.9, 21.9, 22.0, 21.0, 18.7, 18.7, and 26.9.

In some embodiments, the crystalline form is Form 2, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.2, 15.2, 15.3, 20.9, 21.9, 22.0, 21.0, 18.7, 18.7, 26.9, 24.0, 21.1, 27.4, 28.0, 14.7, 20.6, 19.9, 19.4, 21.5, 17.7, 26.0, and 28.3.

In some embodiments, the crystalline form is Form 2, characterized by an XRPD pattern  
15 substantially the same as that shown in FIG. 6.

In some embodiments, Form 2 is a hemi-hydrate.

In some embodiments, the enantiomeric excess (ee) of Form 2 is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%).

In some embodiments, Form 2 is substantially pure.  
20

### *Form 3*

In some embodiments, the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $4.0 \pm 0.2$  degrees  $2\theta$ . For ease of exposition, the aforementioned form is referred to herein as "Form 3." The X-ray powder diffraction pattern of Form 3 can also  
25 include one or more additional characteristic peaks.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $4.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $4.0 \pm 0.2$  degrees  $2\theta$  has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $4.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $4.9 \pm 0.2$  degrees  $2\theta$  has the second highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $25.8 \pm 0.2$  degrees  $2\theta$ .  
30 In some embodiments, the peak at  $25.8 \pm 0.2$  degrees  $2\theta$  has the third highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $21.4 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $21.4 \pm 0.2$  degrees  $2\theta$  has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $9.1 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $9.1 \pm 0.2$  degrees  $2\theta$  has the fifth highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 3 has a peak at  $19.2 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $19.2 \pm 0.2$  degrees  $2\theta$  has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $6.9 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $6.9 \pm 0.2$  degrees  $2\theta$  has the seventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $15.7 \pm 0.2$  degrees  $2\theta$ .  
10 In some embodiments, the peak at  $15.7 \pm 0.2$  degrees  $2\theta$  has the eighth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $16.8 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $16.8 \pm 0.2$  degrees  $2\theta$  has the ninth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $9.9 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $9.9 \pm 0.2$  degrees  $2\theta$  has the tenth highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 3 has a peak at  $14.3 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $14.3 \pm 0.2$  degrees  $2\theta$  has the eleventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $23.9 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $23.9 \pm 0.2$  degrees  $2\theta$  has the twelfth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $6.2 \pm 0.2$  degrees  $2\theta$ . In  
20 some embodiments, the peak at  $6.2 \pm 0.2$  degrees  $2\theta$  has the thirteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $7.5 \pm 0.2$  degrees  $2\theta$ . In  
some embodiments, the peak at  $7.5 \pm 0.2$  degrees  $2\theta$  has the fourteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 3 has a peak at  $31.7 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $31.7 \pm 0.2$  degrees  $2\theta$  has the fifteenth highest relative intensity.

25 In some embodiments, the crystalline form is Form 3, and wherein the XRPD pattern has  
peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 4.0, 4.9, and 25.8.

In some embodiments, the crystalline form is Form 3, and wherein the XRPD pattern has  
peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 4.0, 4.9, 25.8, 21.4, 9.1, 19.2, 6.9, 15.7, 16.8, and 9.9.

In some embodiments, the crystalline form is Form 3, and wherein the XRPD pattern has  
30 peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 4.0, 4.9, 25.8, 21.4, 9.1, 19.2, 6.9, 15.7, 16.8, 9.9, 14.3, 23.9, 6.2, 7.5,  
and 31.7.

In some embodiments, the crystalline form is Form 3, characterized by an XRPD pattern substantially the same as that shown in FIG. 7.

In some embodiments, the crystalline form is Form 3 having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 0.5% to about 5% (e.g., about 1% to about 3%, about 2% to about 3%, or about 2.4%) at about 20 °C to about 180 °C (e.g., about 20 °C to about 170 °C, about 20 °C to about 160 °C, about 20 °C to about 155 °C, about 20 °C to about 150 °C, about 20 °C to about 140 °C, about 40 °C to about 170 °C, about 50 °C to about 160 °C, about 70 °C to about 155 °C, or about 70 °C to about 155 °C. In some embodiments, the crystalline form is Form 3 having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.4% at about 20 °C to about 155 °C.

In some embodiments, the crystalline form is Form 3 having a TGA curve characterized by a weight loss of about 1% to about 10% (e.g., about 2% to about 8%, about 3% to about 7%, about 4% to about 6%, about 4% to about 5%, about 2% to about 8%, about 2% to about 6%, or about 4.5%) at about 110 to about 230 (e.g., about 120 °C to about 220 °C, about 140 °C to about 210 °C, about 150 °C to about 200 °C, or about 155 °C to about 195 °C). In some embodiments, the crystalline form is Form 3 having a TGA curve characterized by a weight loss of about 4.5% at about 155 °C to about 195 °C.

In some embodiments, the crystalline form is Form 3 having a TGA curve that is substantially the same as that shown in FIG. 34.

In some embodiments, the crystalline form is Form 3 having a DSC curve characterized by an endothermic event having an onset temperature of about 162 °C and a peak at about 173 °C. In some embodiments, the crystalline form is Form 3 having a DSC curve characterized by an endothermic event having an onset temperature of about 274 °C and peak at about 283 °C. In some embodiments, the crystalline form is Form 3 having a DSC curve characterized by an endothermic event having an onset temperature of about 162 °C and peak at about 173 °C, and an endothermic event having an onset temperature of about 274 °C and peak at about 283 °C.

In some embodiments, the crystalline form is Form 3 having a TG/DSC thermogram that is substantially the same as that shown in FIG. 34.

In some embodiments, the crystalline form is Form 3 having a TGA curve that is substantially the same as that shown in FIG. 34.

In some embodiments, the crystalline form is Form 3 having a DSC curve that is substantially the same as that shown in FIG. 34.

In some embodiments, the Form 3 is anhydrous.

In some embodiments, the enantiomeric excess (ee) of Form 3 is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%).

In some embodiments, the Form 3 is substantially pure.

#### *Form 4*

In some embodiments, the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $6.3 \pm 0.2$  degrees  $2\theta$  (e.g.,  $6.3 \pm 0.2$  degrees  $2\theta$  and  $20.9 \pm 0.2$  degrees  $2\theta$ ). For ease of exposition, the aforementioned form is referred to herein as "Form 4." The X-ray powder diffraction pattern of Form 4 can also include one or more additional characteristic peaks.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $6.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $6.3 \pm 0.2$  degrees  $2\theta$  has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $20.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.9 \pm 0.2$  degrees  $2\theta$  has the second highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $15.5 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.5 \pm 0.2$  degrees  $2\theta$  has the third highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $24.1 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $24.1 \pm 0.2$  degrees  $2\theta$  has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $21.5 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $21.5 \pm 0.2$  degrees  $2\theta$  has the fifth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $27.7 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $27.7 \pm 0.2$  degrees  $2\theta$  has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $15.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.8 \pm 0.2$  degrees  $2\theta$  has the seventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $14.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $14.9 \pm 0.2$  degrees  $2\theta$  has the eighth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $20.5 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.5 \pm 0.2$  degrees  $2\theta$  has the ninth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $26.9 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $26.9 \pm 0.2$  degrees  $2\theta$  has the tenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $19.9 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $19.9 \pm 0.2$  degrees  $2\theta$  has the eleventh highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 4 has a peak at  $19.3 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $19.3 \pm 0.2$  degrees  $2\theta$  has the twelfth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $28.1 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $28.1 \pm 0.2$  degrees  $2\theta$  has the thirteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $28.4 \pm 0.2$  degrees  $2\theta$ .  
10 In some embodiments, the peak at  $28.4 \pm 0.2$  degrees  $2\theta$  has the fourteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $3.1 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $3.1 \pm 0.2$  degrees  $2\theta$  has the fifteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $27.3 \pm 0.2$  degrees  $2\theta$ .  
15 In some embodiments, the peak at  $27.3 \pm 0.2$  degrees  $2\theta$  has the sixteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $22.1 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $22.1 \pm 0.2$  degrees  $2\theta$  has the seventeenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $25.0 \pm 0.2$  degrees  $2\theta$ .  
20 In some embodiments, the peak at  $25.0 \pm 0.2$  degrees  $2\theta$  has the eighteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $29.1 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $29.1 \pm 0.2$  degrees  $2\theta$  has the nineteenth highest relative intensity.

25 In some embodiments, the XRPD pattern of Form 4 has a peak at  $30.8 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $30.8 \pm 0.2$  degrees  $2\theta$  has the twentieth highest relative intensity.

In some embodiments, the XRPD pattern of Form 4 has a peak at  $19.0 \pm 0.2$  degrees  $2\theta$ .  
In some embodiments, the peak at  $19.0 \pm 0.2$  degrees  $2\theta$  has the twenty-first highest relative intensity.



In some embodiments, the XRPD pattern of Form 4 has a peak at  $18.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $18.0 \pm 0.2$  degrees  $2\theta$  has the twenty-second highest relative intensity.

5 In some embodiments, the crystalline form is Form 4, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 20.9, and 15.5.

In some embodiments, the crystalline form is Form 4, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 20.9, 15.5, 24.1, 21.5, 27.7, 15.8, 14.9, 20.5, and 26.9.

10 In some embodiments, the crystalline form is Form 4, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 20.9, 15.5, 24.1, 21.5, 27.7, 15.8, 14.9, 20.5, 26.9, 19.9, 19.3, 28.1, 28.4, 3.1, 27.3, 22.1, 25.0, 29.1, 30.8, 19.0, and 18.0.

In some embodiments, the crystalline form is Form 4, characterized by an XRPD pattern substantially the same as that shown in FIG. 8.

In some embodiments, the enantiomeric excess (ee) of Form 4 is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%).

15 In some embodiments, the Form 4 is substantially pure.

### *Mesylate Salt*

20 In some embodiments, the crystalline form is a mesylate salt having a TG/DSC thermogram that is substantially the same as that shown in FIG. 14. In some embodiments, the crystalline form is a mesylate salt having a TG/DSC thermogram characterized by one endothermic event with an onset temperature of 200 °C and a peak temperature of 207 °C.

### Methods of Preparing Form 1

25 Methods of preparing (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea can also be found in, e.g., PCT Published Application WO 2022/265993, filed June 13, 2022; and Provisional Application No. 63/532,695, filed on August 15, 2023, both of which are incorporated herein in its entirety.

30 As can be appreciated by the skilled artisan, further methods of synthesizing (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, crystalline forms thereof, and crystalline solvates (e.g., hydrates (e.g., hemi-hydrates)) will be

evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

*Methods of Preparing Form 1*

Form 1 Prepared by Method 1

In some embodiments, the crystalline form is Form 1 prepared by a method comprising:

- (a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in isopropanol to form a solution;
- (b) adding water to the solution to form a mixture;
- (c) reducing the temperature of the mixture then maintaining the temperature for a first period of time;
- (d) increasing the temperature of the mixture then maintaining the temperature for a second period of time;
- (e) reducing the temperature of the mixture then maintaining the temperature for a third period of time; and
- (f) isolating Form 1 from the mixture.

Some embodiments provide a method of preparing a Form 1, comprising:

- (a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in isopropanol to form a solution;
- (b) adding water to the solution to form a mixture;

(c) reducing the temperature of the mixture then maintaining the temperature for a first period of time;

(d) increasing the temperature of the mixture then maintaining the temperature for a second period of time;

5 (e) reducing the temperature of the mixture then maintaining the temperature for a third period of time; and

(f) isolating Form 1 from the mixture.

In some embodiments, Form 1 has one or more characteristics described herein and below.

10 In some embodiments, the XRPD pattern of Form 1 has a peak at  $6.4 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $6.4 \pm 0.2$  degrees  $2\theta$  has the highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $15.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $15.8 \pm 0.2$  degrees  $2\theta$  has the second relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $18.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $18.3 \pm 0.2$  degrees  $2\theta$  has the third highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 1 has a peak at  $22.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $22.3 \pm 0.2$  degrees  $2\theta$  has the fourth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $20.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.8 \pm 0.2$  degrees  $2\theta$  has the fifth highest relative intensity.

20 In some embodiments, the XRPD pattern of Form 1 has a peak at  $19.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $19.3 \pm 0.2$  degrees  $2\theta$  has the sixth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $24.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $24.0 \pm 0.2$  degrees  $2\theta$  has the seventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $26.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $26.9 \pm 0.2$  degrees  $2\theta$  has the eighth highest relative intensity.

25 In some embodiments, the XRPD pattern of Form 1 has a peak at  $14.6 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $14.6 \pm 0.2$  degrees  $2\theta$  has the ninth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $31.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $31.3 \pm 0.2$  degrees  $2\theta$  has the tenth highest relative intensity.

30 In some embodiments, the XRPD pattern of Form 1 has a peak at  $28.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $28.3 \pm 0.2$  degrees  $2\theta$  has the eleventh highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $29.2 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $29.2 \pm 0.2$  degrees  $2\theta$  has the twelfth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $22.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $22.8 \pm 0.2$  degrees  $2\theta$  has the thirteenth highest relative intensity.

5 In some embodiments, the XRPD pattern of Form 1 has a peak at  $28.0 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $28.0 \pm 0.2$  degrees  $2\theta$  has the fourteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $25.3 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $25.3 \pm 0.2$  degrees  $2\theta$  has the fifteenth highest relative intensity.

10 In some embodiments, the XRPD pattern of Form 1 has a peak at  $21.5 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $21.5 \pm 0.2$  degrees  $2\theta$  has the sixteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $19.9 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $19.9 \pm 0.2$  degrees  $2\theta$  has the seventeenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $27.6 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $27.6 \pm 0.2$  degrees  $2\theta$  has the eighteenth highest relative intensity.

15 In some embodiments, the XRPD pattern of Form 1 has a peak at  $20.5 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $20.5 \pm 0.2$  degrees  $2\theta$  has the nineteenth highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $21.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $21.8 \pm 0.2$  degrees  $2\theta$  has the twentieth highest relative intensity.

20 In some embodiments, the XRPD pattern of Form 1 has a peak at  $25.1 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $25.1 \pm 0.2$  degrees  $2\theta$  has the twenty-first highest relative intensity.

In some embodiments, the XRPD pattern of Form 1 has a peak at  $25.8 \pm 0.2$  degrees  $2\theta$ . In some embodiments, the peak at  $25.8 \pm 0.2$  degrees  $2\theta$  has the twenty-second highest relative intensity.

25 In some embodiments, the XRPD pattern of Form 1 has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 15.8, and 18.3.

In some embodiments, the XRPD pattern of Form 1 has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 15.8, 18.3, 22.3, 20.8, 19.3, 24.0, 26.9, 14.6, and 31.3.

30 In some embodiments, the XRPD pattern of Form 1 has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 15.8, 18.3, 22.3, 20.8, 19.3, 24.0, 26.9, 14.6, 31.3, 28.3, 29.2, 22.8, 28.0, 25.3, 21.5, 19.9, 27.6, 20.5, 21.8, 25.1, and 25.8.

In some embodiments, Form 1 is characterized by an XRPD pattern substantially the same as that shown in FIG. 4.

In some embodiments, Form 1 has a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 0.5% to about 5% (e.g., about 1% to about 3%, about 2% to about 3%, or about 2.3%) at about 70 °C to about 140 °C (e.g., about 90 °C to about 130 °C, about 90 °C to about 120 °C, about 90 °C to about 115 °C, about 100 °C to about 140 °C, about 110 °C to about 140 °C, about 100 °C to about 120 °C, about 105 °C to about 120 °C, about 109 °C to about 115 °C, about 75 °C to about 125 °C, about 85 °C to about 113 °C, about 85 °C to about 105 °C, or about 112 °C. In some embodiments, the Form 1 has a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.3% at about 112.5 °C. In some  
10      embodiments, Form 1 has a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.3% at about 85 °C to about 113 °C.

In some embodiments, Form 1 has a TGA curve characterized by a weight loss of about 5% to about 30% (e.g., about 5% to about 27%, about 5% to about 25%, about 5% to about 22%, about 10% to about 25%, about 20% to about 22%, about 14% to about 20%, or about 17.6%) at about 150 °C to about 250 °C (e.g., about 230 to about 260 °C about 230 °C to about 250 °C, about 162 °C to about 248 °C, about 230 °C to about 240 °C, about 240 °C to about 260 °C, about 240 °C to about 250 °C, about 242 °C to about 248 °C, or about 245 °C). In some embodiments, Form 1 has a TGA curve characterized by a weight loss of about 17.6% at about 245 °C. In  
15      some embodiments, the Form 1 has a TGA curve characterized by a weight loss of about 17.6% at about 162 °C to about 248 °C.

In some embodiments, the Form 1 has a TGA curve that is substantially the same as that shown in FIG. 28. In some embodiments, the crystalline form is Form 1 having a Thermal Gravimetric/Differential Scanning Calorimetry (TG/DSC) thermogram that is substantially the same as that shown in FIG. 28.  
25

In some embodiments, the Form 1 has a differential scanning calorimetry (DSC) first heat cycle thermogram having an endothermic event having an onset temperature of about 105 °C and a peak of about 129 °C, an endothermic event having an onset temperature of about 158 °C and a peak of about 162 °C and an endothermic event having an onset temperature of about 174 °C and a peak of about 177 °C.  
30

In some embodiments, the Form 1 has a Differential Scanning Calorimetry (DSC) thermogram that is substantially the same as that shown in FIG. 29.

In some embodiments, the Form 1 has a DSC first cooling cycle thermogram characterized by a single exothermic event at with an onset temperature of 151 °C and a peak temperature of 147 °C.

In some embodiments, the Form 1 has a DSC first cooling cycle thermogram substantially the same as that shown in FIG. 30.

In some embodiments, the Form 1 is a hemi-hydrate.

In some embodiments, the enantiomeric excess (ee) of crystalline Form 1 is at least 90% (e.g., at least 92%, at least 94%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100%).

In some embodiments, the Form 1 is substantially pure.

In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof comprises the free base of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof is the free base of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof comprises amorphous (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof is amorphous (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof comprises the free base amorphous form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or

solvate thereof is the free base amorphous form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof comprises Form 1\*. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof is Form 1\*.

In some embodiments, the dissolving in step (a) is performed at about 40 °C to 60 °C (e.g., about 45 °C to about 55 °C, or about 50 °C). In some embodiments, the dissolving in step (a) is performed at about 50 °C.

In some embodiments, the solution formed in step (a) has a concentration of about 0.08 g/mL to about 1.65 g/mL (e.g., about 0.09 g/mL to about 1.55 g/mL, about 0.1 g/mL to about 0.145 g/mL, about 0.1 g/mL to about 0.135 g/mL, about 0.12 g/mL to about 0.13 g/mL, or about 0.125 g/mL). In some embodiments, the solution formed in step (a) has a concentration of about 0.125 g/mL.

In some embodiments, step (a) comprises cooling the solution to about 30 °C to 50 °C (e.g., about 35 °C to about 45 °C, or about 40 °C). In some embodiments, step (a) comprises cooling the solution to about 40 °C. In some embodiments, the cooling is performed at about 0.1 °C per minute to about 5 °C per minute (e.g., about 0.5 °C per minute to about 2 °C per minute, or about 1 °C per minute). In some embodiments, the cooling is performed at about 1 °C per minute.

In some embodiments, the volume/volume ratio of water added to the solution in step (b) to the isopropanol used in the dissolving in step (a) is about 2:1 to about 6:1 (e.g., about 3:1 to about 5:1, or about 4:1). In some embodiments, the volume/volume ratio of water added to the solution in step (b) to the isopropanol used in the dissolving in step (a) is about 4:1.

In some embodiments, about 1/8<sup>th</sup> to about 1/32<sup>nd</sup> of the water is added to the solution per hour. 1/16<sup>th</sup> of the water is added to the solution per hour. In some embodiments, about 1/16<sup>th</sup> of the water is added to the solution per hour.

In some embodiments, the temperature of the mixture in step (c) is reduced to about 1 °C to about 15 °C (e.g., about 1 °C to about 10 °C, about 2 °C to about 8 °C, about 3 °C to about 7 °C, or about 5 °C). In some embodiments, the temperature of the mixture in step (c) is reduced to about 5 °C. In some embodiments, the first period of time is about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours, about 1 minute to about

6 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 1 minute to about 30 minutes, about 1 minute to about 5 minutes, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, about 1 minute, or about 1 hour). In some embodiments, the first period of time is about 1 hour. In some embodiments, the first period of time is about 1 minute.

5           In some embodiments, the temperature of the mixture in step (d) is increased to about 25 °C to about 60 °C (e.g., about 25 °C to about 50 °C, about 30 °C to about 60 °C, about 30 °C to about 50 °C, about 35 °C to about 45 °C, or about 5 °C). In some embodiments, the temperature of the mixture in step (c) is increased to about 40 °C. In some embodiments, the second period of time is about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute  
10       to about 12 hours, about 1 minute to about 6 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 1 minute to about 30 minutes, about 1 minute to about 5 minutes, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, about 1 minute, or about 1 hour). In some embodiments, the second period of time is about 1 hour. In some embodiments, the second period of time is about 1 minute.

15           In some embodiments, the temperature of the mixture in step (e) is reduced to about 1 °C to about 15 °C (e.g., about 1 °C to about 10 °C, about 2 °C to about 8 °C, about 3 °C to about 7 °C, or about 5 °C). In some embodiments, the temperature of the mixture in step (e) is reduced to about 5 °C. In some embodiments, the third period of time is about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours, about 1 minute to about  
20       6 hours, about 1 minute to about 3 hours, about 1 minute to about 2 hours, about 1 minute to about 30 minutes, about 1 minute to about 5 minutes, about 30 minutes to about 1.5 hours, about 45 minutes to about 1.25 hours, about 6 hours to about 18 hours, about 6 hours to about 24 hours, about 9 hours to about 15 hours, about 9 hours to about 14 hours, about 10 hours to about 12 hours, about 10.5 hours to about 11.5 hours, about 11 hours, about 12 hours, about 1 hour, or about 1  
25       minute). In some embodiments, the third period of time is about 11 hours. In some embodiments, the third period of time is about 11 hours.

          In some embodiments, step (f) comprises filtering the mixture to provide Form 1. In some embodiments, step (f) comprises filtering the mixture to provide a solid; and rinsing the solid to provide Form 1. In some embodiments, rinsing the solid to provide Form 1 comprises drying the  
30       solid after the rinsing to provide Form 1. In some embodiments, the rinsing the solid comprises rinsing the solid with a solvent. In some embodiments, the solvent comprises an alcohol. In some



embodiments, the alcohol is methanol, ethanol, and/or isopropanol. In some embodiments, the solvent comprises water. In some embodiments, the solvent comprises an alcohol and water. In some embodiments, the solvent comprises methanol and water. In some embodiments, the solvent is methanol and water.

5 In some embodiments, step (f) comprises:  
filtering the mixture to provide a solid;  
rinsing the solid with methanol and water; and  
drying the solid to provide Form 1.

In some embodiments, the drying is performed for about 1 minute to about 16 hours (e.g.,  
10 about 1 minute to about 14 hours, about 1 minute to about 12 hours, about 1 minute to about 8  
hours, about 1 minute to about 4 hours, about 1 minute to about 2 hours, about 1 minute to about  
1 hour, or about 1 minute to about 30 minutes. In some embodiments, drying the solid comprises  
drying the solid at a pressure lesser than atmospheric pressure. In some embodiments, the drying  
is performed at a temperature of about 25 °C to about 100 °C (e.g., about 25 °C to about 80 °C,  
15 about 35 °C to about 80 °C, about 45 °C to about 70 °C, about 45 °C to about 60 °C).

#### Form 1 Prepared by Method 2

In some embodiments, the crystalline form is Form 1 prepared by a method comprising:  
dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-  
20 2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in methanol  
to form a solution;  
adding water to the solution to form a first mixture;  
adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-  
2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture; and  
25 isolating a solid from the third mixture to provide Form 1.

Some embodiments provide a method of preparing Form 1 comprising:  
dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-  
2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in methanol  
30 to form a solution;  
adding water to the solution to form a first mixture;

adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture; and  
isolating a solid from the third mixture to provide Form 1.

5 In some embodiments, the crystalline form is Form 1 prepared by a method comprising:

(a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in methanol to form a solution;

(b) adding water to the solution to form a first mixture;

10 (c) adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture;

(d) agitating the second mixture;

(e) adding water to the second mixture to form a third mixture;

(f) agitating the third mixture; and

15 (g) isolating Form 1 from the third mixture.

Some embodiments provide a method of preparing Form 1 comprising:

(a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in methanol to form a solution;

20

(b) adding water to the solution to form a first mixture;

(c) adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture;

(d) agitating the second mixture;

25 (e) adding water to the second mixture to form a third mixture;

(f) agitating the third mixture; and

(g) isolating Form 1 from the third mixture.

30 In some embodiments, the solution formed in step (a) has a concentration of about 0.03 g/mL to about 1 g/mL (e.g., about 0.03 g/mL to about 0.5 g/mL, about 0.05 g/mL to about 0.3 g/mL, about 0.1 g/mL to about 0.2 g/mL, about 0.13 g/mL to about 0.18 g/mL, or about 0.16

g/mL). In some embodiments, the solution formed in step (a) has a concentration of about 0.16 g/mL.

In some embodiments, dissolving the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in methanol to form a solution comprises dissolving the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in a first portion of methanol to form an unfiltered solution, filtering the unfiltered solution through a filter to provide a filtrate, then rinsing the filter with a second portion of methanol to provide a rinse that is combined with the filtrate to provide the solution. In some embodiments, the filtering is a polish filtering. In some embodiments, the filter has a pore size of about 0.2 microns. In some embodiments, the weight of the first portion of methanol is about 4 to about 8 times (e.g., about 5 to about 8 times, about 6 to about 7 times, or about 6.3 times (e.g., about 6.3 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved. In some embodiments, the weight of the first portion of methanol is about 4 to about 8 times (e.g., about 0.5 to about 3 times, about 1 to about 3 times, or about 1.6 times (e.g., about 1.6 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved.

In some embodiments, the solution is cooled to about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C, about 20 °C to about 25 °C, about 17 °C to about 23 °C, about 15 °C, about 20 °C, or about 25 °C (e.g., about 15 °C to about 25 °C)) before adding the water in step (b). In some embodiments, the water added in step (b) is purified water. In some embodiments, adding the water in step (b) comprises filtering the water through a filter, then adding the water to form the first mixture. In some embodiments, the water added in step (b) is about 0.1 to about 2 times (e.g., about 0.1 to about 1.5 times, about 0.1 to about 1 times, about 0.3 to about 0.7 times, or about 0.5 times (e.g., about 0.5 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a).

In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 added in step (c) is about 0.1% to about 20% by weight (e.g., about 0.1% to about 15% by weight, about 0.1% to about 10% by weight, about 0.1% to about 5% by weight, about 0.1% to about 3% by weight, about 0.5% to about 3%

by weight, about 0.7% to about 2.5% by weight, about 0.7% to about 1.3% by weight, or about 1% by weight (e.g., about 1% by weight)) of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a).

In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 added in step (c) is prepared by Method 1 described herein. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 added in step (c) is prepared by Method 2 described herein.

In some embodiments, the agitating in step (d) is performed at about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C, about 20 °C to about 25 °C, about 17 °C to about 23 °C, about 15 °C, about 20 °C, or about 25 °C (e.g., about 15 °C to about 25 °C)). In some embodiments, the agitating in step (d) is performed for about 1 minute to about 24 hours (e.g., about 1 minute to about 18 hours, about 1 minute to about 12 hours, about 1 minute to about 8 hours, about 1 minute to about 6 hours, about 30 minutes to about 6 hours, about 1 hour to about 5 hours, about 2 hours to about 4 hours, about 2.5 hours to about 3.5 hours, or about 3 hours (e.g., about 3 hours)).

In some embodiments, the water added in step (e) is purified water. In some embodiments, adding the water in step (e) comprises filtering the water through a filter, then adding the water to form the third mixture. In some embodiments, the water added in step (e) is about 0.1 to about 20 times (e.g., about 0.1 to about 15 times, about 0.1 to about 10 times, about 1 to about 9 times, about 3 to about 7 times, about 4 to about 5 times, or about 4.5 times (e.g., about 4.5 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a). In some embodiments, the water added in step (e) is added over a period of about 1 second to about 48 hours (e.g., about 1 minute to about 24 hours, about 1 minute to about 18 hours, about 1 hour to about 12 hours, about 4 hours to about 12 hours, about 6 hours to about 10 hours, about 7 hours to about 9 hours, or about 8 hours (e.g., about 8 hours)).

In some embodiments, the agitating in step (f) is performed at about 5 °C to about 35 °C (e.g., about 10 °C to about 30 °C, about 15 °C to about 25 °C, about 15 °C to about 20 °C, about 20 °C to about 25 °C, about 17 °C to about 23 °C, about 15 °C, about 20 °C, or about 25 °C (e.g., about 15 °C to about 25 °C)). In some embodiments, the agitating in step (f) is performed for about 1

minute to about 48 hours (e.g., about 1 minute to about 36 hours, about 1 minute to about 24 hours, about 4 hours to about 24 hours, about 8 hours to about 20 hours, about 12 hours to about 20 hours, about 14 hours to about 18 hours, about 15 hours to about 17 hours, or about 16 hours (e.g., about 16 hours)).

5 In some embodiments, step (f) comprises filtering the mixture to provide Form 1. In some embodiments, step (f) comprises filtering the mixture to provide a solid; and rinsing the solid to provide Form 1. In some embodiments, rinsing the solid to provide Form 1 comprises drying the solid after the rinsing to provide Form 1. In some embodiments, the rinsing the solid comprises rinsing the solid with a solvent. In some embodiments, the solvent comprises an alcohol. In some  
10 embodiments, the alcohol is methanol, ethanol, and/or isopropanol. In some embodiments, the solvent comprises water. In some embodiments, the solvent comprises an alcohol and water. In some embodiments, the solvent comprises methanol and water. In some embodiments, the solvent is methanol and water.

In some embodiments, isolating Form 1 from the third mixture comprises:

- 15 (i) filtering the third mixture to provide a solid;  
(ii) rinsing the solid with methanol and water; and  
(iii) drying the solid to provide Form 1.

In some embodiments, the weight of the methanol and water is about 0.5 to about 5 times (e.g., about 0.5 to about 4 times, about 0.5 to about 3 times, about 1 to about 3 times, about 1.5 to  
20 about 2.1 times, or about 1.8 times (e.g., about 1.8 times)) the weight of the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea that is dissolved in step (a). In some embodiments, the ratio of methanol to water is about 1:100 to about 100:1 (e.g., about 20:80 to about 90:10, about 30:70 to about 90:10, about 50:50 to about 80:20, about 55:45 to about 65:35, or about 61:39 (e.g., about 61:39)).

25 In some embodiments, drying the solid comprises drying the solid at about 30 °C to about 60 °C (e.g., about 30 °C to about 50 °C, about 35 °C to about 45 °C, about 35 °C to about 40 °C, about 40 °C to about 45 °C, about 35 °C, about 40 °C, or about 45 °C (e.g., about 35 °C to about 45 °C)). In some embodiments, drying the solid comprises drying the solid at a pressure lesser than atmospheric pressure. In some embodiments, drying the solid comprises drying the solid  
30 under an inert gas (e.g., nitrogen or argon (e.g., nitrogen)). In some embodiments, drying the solid comprises drying the solid until the solid includes about 1% to about 4% (e.g., about 1.5% to about

3.2% or about 2% to about 2.6% (e.g., about 2% to about 2.6%) by weight of water. In some embodiments, the Form 1 obtained in step (g) includes about 1% to about 4% (e.g., about 1.5% to about 3.2% or about 2% to about 2.6% (e.g., about 2% to about 2.6%) by weight of water.

## 5 **Pharmaceutical Compositions and Administration**

### *General*

In some embodiments, the 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate is administered as a pharmaceutical composition that includes the chemical entity and one  
10 or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein. In some embodiments, the 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate is a pharmaceutically acceptable salt. In some embodiments, the 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a  
15 pharmaceutically acceptable salt and/or solvate is a pharmaceutically acceptable solvate. In some embodiments, the 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate is a pharmaceutically acceptable solvate of a salt.

In some embodiments, the chemical entities can be administered in combination with one  
20 or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- $\alpha$ -tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as  
25 phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block  
30 polymers, and wool fat. Cyclodextrins such as  $\alpha$ -,  $\beta$ -, and  $\gamma$ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- $\beta$ -cyclodextrins,

or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the balance made up from pharmaceutically acceptable excipients may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity  
5 provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22<sup>nd</sup> Edition (Pharmaceutical Press, London, UK. 2012).

10 *Routes of Administration and Composition Components*

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal,  
15 intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intra gingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric,  
20 oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In certain embodiments, the route of administration is oral.

In other embodiments, the compounds described herein or a pharmaceutical composition thereof are suitable for local delivery to the digestive or GI tract by way of oral administration  
25 (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders  
30 such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium

carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such pharmaceutically acceptable excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

In some embodiments, the pharmaceutical composition is in the form of a tablet. In some embodiments, the pharmaceutical composition is in the form of a capsule.

In some embodiments, the pharmaceutical composition comprises 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, and one or more pharmaceutically acceptable carriers. In some embodiments, the pharmaceutical composition comprises (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, and one or more pharmaceutically acceptable carriers. In some embodiments, the pharmaceutical composition comprises (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, and one or more pharmaceutically acceptable carriers. In some embodiments, the pharmaceutical composition comprises 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate, and one or



more pharmaceutically acceptable carriers. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is crystalline. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is a solvate. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is a hydrate. In some  
5       embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is a hemi-hydrate. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1. In some  
10       embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1\*. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 2. In some  
embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 3. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 4.

15       In some embodiments, the tablet comprises granules. In some embodiments, the tablet comprises granules and extragranular matter. In some embodiments, the tablet is surrounded by a layer.

      In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg,  
20       about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

      In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg,  
25       about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

      In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg,  
30       about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1

mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of a pharmaceutically acceptable solvate of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hemi-hydrate.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg, of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1. In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1\*.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg,

about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-

2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about

70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate. In some embodiments, the pharmaceutical composition comprises about 5 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate. In some embodiments, the pharmaceutical composition comprises about 20 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-

3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate. In some embodiments, the pharmaceutical composition comprises about 5 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate. In some embodiments, the pharmaceutical composition comprises about 20 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate. In some embodiments, the pharmaceutical composition comprises about 5 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate. In some embodiments, the pharmaceutical composition comprises about 20 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate. In some embodiments, the pharmaceutical composition comprises about 5 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate. In some embodiments, the pharmaceutical composition comprises about 20 mg of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of hemihydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of crystalline (R)-Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of crystalline (R)-Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-



(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 20 mg of crystalline (R)-Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 1 mg to about 100 mg (e.g.,  
5 about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg,  
10 about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg) of crystalline (R)-Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical composition comprises about 5 mg of crystalline (R)-Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the pharmaceutical  
15 composition comprises about 20 mg of crystalline (R)-Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea.

In some embodiments, the pharmaceutical composition comprises 1 mg of Form 1, as described herein. In some embodiments, the pharmaceutical composition comprises 1 mg of Form 1\*, as described herein. In some embodiments, the pharmaceutical composition comprises 5 mg  
20 of Form 1, as described herein. In some embodiments, the pharmaceutical composition comprises 5 mg of Form 1\*, as described herein. In some embodiments, the pharmaceutical composition comprises 10 mg of Form 1, as described herein. In some embodiments, the pharmaceutical composition comprises 10 mg of Form 1\*, as described herein. In some embodiments, the pharmaceutical composition comprises 20 mg of Form 1, as described herein. In some  
25 embodiments, the pharmaceutical composition comprises 20 mg of Form 1\*, as described herein. In some embodiments, the pharmaceutical composition comprises 25 mg of Form 1, as described herein. In some embodiments, the pharmaceutical composition comprises 25 mg of Form 1\*, as described herein.

In some embodiments, the 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the 1-(2-  
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aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is crystalline. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is a hydrate. In some embodiments, the 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is hemi-hydrate (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea. In some embodiments, the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1.

In some embodiments, the composition comprises microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate, or any combination thereof. In some embodiments, the composition comprises microcrystalline cellulose. In some embodiments, the composition comprises mannitol. In some embodiments, the composition comprises croscarmellose sodium. In some embodiments, the composition comprises colloidal silicon dioxide. In some embodiments, the composition comprises sodium stearyl fumarate.

In some embodiments, the weight percentage of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (e.g., (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea) in the composition is about 0.1% to about 50% (e.g., about 0.1% to about 40%, about 0.1% to about 30%, about 0.1% to about 25%, about 0.1% to about 20%, about 0.1% to about 15%, about 1% to about 10%, about 1% to about 9%, about 1% to about 5%, about 5% to about 10%, about 3% to about 7%, about 4% to about 6%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10%). In some embodiments, the weight percentage of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea (e.g., (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea) in the composition is about 5%.

In some embodiments, the weight percentage of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in the composition is about 0.1% to about 50% (e.g., about 0.1% to about 40%, about 0.1% to about 30%, about 0.1% to about 25%, about 0.1% to about 20%, about 0.1% to about 15%, about 1% to about 10%, about 1% to about

9%, about 1% to about 5%, about 5% to about 10%, about 3% to about 7%, about 4% to about 6%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10%). In some embodiments, the weight percentage of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in the composition is about 5%.

In some embodiments, the weight percentage of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in the composition is about 0.1% to about 50% (e.g., about 0.1% to about 40%, about 0.1% to about 30%, about 0.1% to about 25%, about 0.1% to about 20%, about 0.1% to about 15%, about 1% to about 10%, about 1% to about 9%, about 1% to about 5%, about 5% to about 10%, about 3% to about 7%, about 4% to about 6%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10%). In some embodiments, the weight percentage of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in the composition is about 5%.

In some embodiments, the weight percentage of microcrystalline cellulose in the composition is about 20% to about 70% (e.g., about 30% to about 60%, about 35% to about 55%, about 40% to about 50%, about 43% to about 47%, about 44%, about 45%, or about 44.6%). In some embodiments, the weight percentage of microcrystalline cellulose in the composition is about 44.6%.

In some embodiments, the weight percentage of mannitol in the composition is about 20% to about 70% (e.g., about 30% to about 60%, about 35% to about 55%, about 40% to about 50%, about 43% to about 47%, about 44%, about 45%, or about 44.9%). In some embodiments, the weight percentage of mannitol in the composition is about 44.9%.

In some embodiments, the weight percentage of croscarmellose sodium in the composition is about 0.1% to about 15% (e.g., about 0.1% to about 10%, about 0.1% to about 8%, about 1% to about 6%, about 1% to about 5%, about 2% to about 4%, or about 3%). In some embodiments, the weight percentage of croscarmellose sodium in the composition is about 3%.

In some embodiments, the weight percentage of colloidal silicon dioxide in the composition is about 0.1% to about 15% (e.g., about 0.1% to about 10%, about 0.1% to about 7%, about 0.1% to about 5%, about 0.1% to about 3%, about 0.1% to about 2%, about 0.5% to about 2%, about 0.75% to about 1.75%, about 1% to about 1.5%, about 1%, about 2%, or about 1.25%).

In some embodiments, the weight percentage of colloidal silicon dioxide in the composition is about 1.25%.

In some embodiments, the weight percentage of sodium stearyl fumarate in the composition is about 0.1% to about 15% (e.g., about 0.1% to about 10%, about 0.1% to about 7%, about 0.1% to about 5%, about 0.1% to about 3%, about 0.1% to about 2%, about 0.5% to about 2%, about 0.75% to about 1.75%, about 1% to about 1.5%, about 1%, about 2%, or about 1.25%). In some embodiments, the weight percentage of sodium stearyl fumarate in the composition is about 1.25%.

In some embodiments (for example, when the composition is in the form of a tablet surrounded by a layer), the weight percentage of the layer in the composition is about 0.2% to about 6% (e.g., about 1% to about 5%, about 2% to about 4%, or about 3%). In some embodiments (when the composition is in the form of a tablet surrounded by a layer), the weight percentage of the layer in the composition is about 3%.

In some embodiments, the pharmaceutical composition is in the form of a tablet; the weight percentage of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in the composition is about 0.1% to about 30%; the weight percentage of microcrystalline cellulose in the composition is about about 35% to about 55%; the weight percentage of mannitol in the composition is about about 35% to about 55%; the weight percentage of croscarmellose sodium in the composition is about about 1% to about 5%; the weight percentage of colloidal silicon dioxide in the composition is about about 0.1% to about 3%; and the weight percentage of sodium stearyl fumarate in the composition is about 0.1% to about 5%.

In some embodiments, the pharmaceutical composition is in the form of a tablet; the weight percentage of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea in the composition is about 5%; the weight percentage of microcrystalline cellulose in the composition is about 44.6%; the weight percentage of mannitol in the composition is about 44.9%; the weight percentage of croscarmellose sodium in the composition is about 3%; the weight percentage of colloidal silicon dioxide in the composition is about 1.25%; and the weight percentage of sodium stearyl fumarate in the composition is about 1.25%.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action

of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments, the pharmaceutically acceptable excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage forms, pharmaceutically acceptable excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

In certain embodiments, solid oral dosage forms can further include one or more components that chemically and/or structurally predispose the composition for delivery of the chemical entity to the stomach or the lower GI; e.g., the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, e.g., Filipinski, K.J., et al., 2013, 13, 776-802, which is incorporated herein by reference in its entirety.

Some embodiments provide a solid dosage form for oral administration comprising Form 1, as described herein. Some embodiments provide a solid dosage form for oral administration comprising Form 1\*, as described herein. In some embodiments, the solid dosage form for oral administration is a tablet. In some embodiments, the solid dosage form for oral administration is a capsule.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and pharmaceutically acceptable excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient may be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate, Eudragit series (methacrylic acid-methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes.

Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof. Intratumoral injections are discussed, e.g., in Lammers, et al., *Neoplasia*. **2006**, *10*, 788–795.

Pharmaceutically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM), lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the chemical entities described herein with suitable non-irritating pharmaceutically acceptable excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

Ocular compositions can include, without limitation, one or more of any of the following: viscosogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic,

cationic or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

### *Dosages*

The dosages may be varied depending on, for example, the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, a dose of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1



mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg). In some embodiments, the crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1. In some embodiments, the crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is Form 1\*.

In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of hemi-hydrate Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of Form 1\* (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 500 mg (e.g., about 1 mg to about 450 mg, about 1 mg to about 400 mg, about 1 mg to about 350 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, or about 1 mg to about 50 mg).

In some embodiments, a dose of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about

10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 5 mg. In some embodiments, a dose of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 20 mg.

In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 5 mg. In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 20 mg.

In some embodiments, a dose of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 5 mg. In some embodiments, a dose of (S)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 20 mg.

In some embodiments, a dose of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 5 mg. In some embodiments, a dose of crystalline (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 20 mg.

In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate is about 5 mg. In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea solvate is about 20 mg.

In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg,

about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate is about 5 mg. In some embodiments, a dose of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea hydrate is about 20 mg.

In some embodiments, a dose of hemi-hydrate Form 1 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of hemi-hydrate Form 1 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 5 mg. In some embodiments, a dose of hemi-hydrate Form 1 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 20 mg.

In some embodiments, a dose of Form 1\* (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 1 mg to about 100 mg (e.g., about 1 mg to about 90 mg, about 1 mg to about 80 mg, about 1 mg to about 70 mg, about 1 mg to about 60 mg, about 1 mg to about 40 mg, about 1 mg to about 35 mg, about 1 mg to about 30 mg, about 1 mg to about 25 mg, about 1 mg to about 20 mg, about 5 mg to about 20 mg, about 1 mg to about 10 mg, about 15 mg to about 25 mg, about 3 mg to about 7 mg, about 18 mg to about 22 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, or about 50 mg). In some embodiments, a dose of Form 1\* (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 5 mg. In some embodiments, a dose of Form 1\* (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is about 20 mg.

In some embodiments, the total daily dose is 1 mg of Form 1, as described herein. In some embodiments, the total daily dose is 1 mg of Form 1\*, as described herein. In some embodiments,

the total daily dose is 5 mg of Form 1, as described herein. In some embodiments, the total daily dose is 5 mg of Form 1\*, as described herein. In some embodiments, the total daily dose is 10 mg of Form 1, as described herein. In some embodiments, the total daily dose is 10 mg of Form 1\*, as described herein. In some embodiments, the total daily dose is 20 mg of Form 1, as described herein. In some embodiments, the total daily dose is 20 mg of Form 1\*, as described herein. In some embodiments, the total daily dose is 25 mg of Form 1, as described herein. In some embodiments, the total daily dose is 25 mg of Form 1\*, as described herein.

### *Regimens*

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

In some embodiments, the compounds and compositions described herein are administered once daily. In some embodiments, the compounds and compositions described herein are administered twice daily.

In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a

period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

## **Methods of Treatment**

### *Indications*

The crystalline forms of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salts and/or solvates thereof, is useful for treating diseases and disorders which can be treated with a PI3K $\alpha$  inhibitor, such as PI3K $\alpha$ -associated diseases and disorders, e.g., PIK3CA-related overgrowth syndromes (PROS), vascular malformation, and proliferative disorders such as cancers, including hematological cancers and solid tumors (e.g., advanced or metastatic solid tumors).

In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same (a PI3K $\alpha$ -associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). For example, the subject has a tumor that is positive for a mutation as described in Table 1 or Table 2. The subject can be a subject with a tumor(s) that is positive for a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a PI3K $\alpha$ -associated cancer. In some embodiments, the subject has a clinical

record indicating that the subject has a tumor that has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

In some embodiments, the subject is a pediatric subject.

5       The term “pediatric subject” as used herein refers to a subject under the age of 21 years at the time of diagnosis or treatment. The term “pediatric” can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)).

10   Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. Rudolph’s Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to

15   less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age

20   to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

In certain embodiments, 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salts and/or solvates thereof, are useful for preventing diseases and disorders as defined herein (for example, PIK3CA-related overgrowth syndromes (PROS) and cancer). The term “preventing” as used herein means to delay the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

30       The term “PI3K $\alpha$ -associated disease or disorder” as used herein refers to diseases or disorders associated with or having a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the

expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a *PIK3CA* gene, or a PI3K $\alpha$  protein, or the expression or activity or level of any of the same described herein). Non-limiting examples of a PI3K $\alpha$ -associated disease or disorder include, for example, PIK3CA-related overgrowth syndromes (PROS), brain disorders (e.g., as  
5 macrocephaly-capillary malformation (MCAP) and hemimegalencephaly), lymphatic malformations (LMs), cavernous malformations (CMs), congenital lipomatous (e.g., overgrowth of vascular malformations), epidermal nevi and skeletal/spinal anomalies (e.g., CLOVES syndrome) and fibroadipose hyperplasia (FH), or cancer (e.g., PI3K $\alpha$ -associated cancer).

Some embodiments provide a method of treating PIK3CA-related overgrowth syndromes  
10 (PROS) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

Some embodiments provide a method of treating macrocephaly-capillary malformation  
15 (MCAP) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

Some embodiments provide a method of treating hemimegalencephaly in a subject in need  
20 thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

Some embodiments provide a method of treating lymphatic malformations (LMs) in a  
25 subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

Some embodiments provide a method of treating congenital lipomatous in a subject in need  
30 thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.



Some embodiments provide a method of treating epidermal nevi in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

5        Some embodiments provide a method of treating CLOVES syndrome in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

10       Some embodiments provide a method of treating fibroadipose hyperplasia (FH) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

15       Some embodiments provide a method of treating cavernous malformations (CMs) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

The term “PI3K $\alpha$ -associated cancer” as used herein refers to cancers associated with or having a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same. Non-limiting examples of PI3K $\alpha$ -associated cancers are described herein.

20       The phrase “dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same” refers to a genetic mutation (e.g., a mutation in a *PIK3CA* gene that results in the expression of a PI3K $\alpha$  that includes a deletion of at least one amino acid as compared to a wild type PI3K $\alpha$ , a mutation in a *PIK3CA* gene that results in the expression of PI3K $\alpha$  with one or more point mutations as compared to a wild type PI3K $\alpha$ , a mutation in a *PIK3CA* gene that results in the expression of PI3K $\alpha$  with at least one inserted amino acid as compared to a wild type PI3K $\alpha$ , a gene duplication that results in an increased level of PI3K $\alpha$  in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of PI3K $\alpha$  in a cell), an alternative spliced version of PI3K $\alpha$  mRNA that results in PI3K $\alpha$  having a deletion of at least one amino acid in the PI3K $\alpha$  as compared to the wild type PI3K $\alpha$ ), or increased expression (e.g., increased levels) of a wild type PI3K $\alpha$  in a mammalian cell due to aberrant cell signaling and/or dysregulated autocrine/paracrine signaling (e.g., as compared to a control non-

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cancerous cell). As another example, a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same, can be a mutation in a *PIK3CA* gene that encodes a PI3K $\alpha$  that is constitutively active or has increased activity as compared to a protein encoded by a *PIK3CA* gene that does not include the mutation. Non-limiting examples of PI3K $\alpha$  point mutations/substitutions/insertions/deletions are described in Table 1 and Table 2.

The term “activating mutation” in reference to PI3K $\alpha$  describes a mutation in a *PIK3CA* gene that results in the expression of PI3K $\alpha$  that has an increased kinase activity, e.g., as compared to a wild type PI3K $\alpha$ , e.g., when assayed under identical conditions. For example, an activating mutation can be a mutation in a *PIK3CA* gene that results in the expression of a PI3K $\alpha$  that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acid substitutions (e.g., any combination of any of the amino acid substitutions described herein) that has increased kinase activity, e.g., as compared to a wild type a PI3K $\alpha$ , e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in a *PIK3CA* that results in the expression of a PI3K $\alpha$  that has one or more (e.g., two, three, four, five, six, seven, eight, nine, or ten) amino acids deleted, e.g., as compared to a wild type PI3K $\alpha$ , e.g., when assayed under identical conditions. In another example, an activating mutation can be a mutation in a *PIK3CA* gene that results in the expression of a PI3K $\alpha$  that has at least one (e.g., at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 14, at least 16, at least 18, or at least 20) amino acid inserted as compared to a wild type PI3K $\alpha$ , e.g., the exemplary wild type PI3K $\alpha$  described herein, e.g., when assayed under identical conditions. Additional examples of activating mutations are known in the art.

The term “wild type” or “wild-type” describes a nucleic acid (e.g., a *PIK3CA* gene or a PI3K $\alpha$  mRNA) or protein (e.g., a PI3K $\alpha$ ) sequence that is typically found in a subject that does not have a disease or disorder related to the reference nucleic acid or protein.

The term “wild type PI3K $\alpha$ ” or “wild-type PI3K $\alpha$ ” describes a normal PI3K $\alpha$  nucleic acid (e.g., a *PIK3CA* or PI3K $\alpha$  mRNA) or protein that is found in a subject that does not have a PI3K $\alpha$ -associated disease, e.g., a PI3K $\alpha$ -associated cancer (and optionally also does not have an increased risk of developing a PI3K $\alpha$ -associated disease and/or is not suspected of having a PI3K $\alpha$ -associated disease), or is found in a cell or tissue from a subject that does not have a PI3K $\alpha$ -associated disease, e.g., a PI3K $\alpha$ -associated cancer (and optionally also does not have an increased

risk of developing a PI3K $\alpha$ -associated disease and/or is not suspected of having a PI3K $\alpha$ -associated disease).

Provided herein is a method of treating cancer (e.g., a PI3K $\alpha$ -associated cancer) in a subject in need of such treatment, the method comprising administering to the subject a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof. For example, provided herein are methods for treating PI3K $\alpha$ -associated cancer in a subject in need of such treatment, the method comprising a) detecting a dysregulation of *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same includes one or more a PI3K $\alpha$  protein substitutions/point mutations/insertions. Non-limiting examples of PI3K $\alpha$  protein substitutions/insertions/deletions are described in Table 1 and Table 2.

In some embodiments, the subject was determined to have one or more mutations in the kinase domain of the PI3K $\alpha$  protein. In some embodiments, the subject was determined to have one or more mutations in the helical domain of the PI3K $\alpha$  protein. In some embodiments, the subject was determined to have one or more mutations in each of the kinase domain and the helical domain of the PI3K $\alpha$  protein.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletion is selected from the group consisting of E542A, E542G, E542K, E542Q, E542V, E542S, E542R, E542I, E542L, E545A, E545D, E545G, E545K, E545Q, E545V, E545R, E545T, Q546K, Q546R, Q546P, Q546E, Q546H, E726K, N1044K, N1044Y, N1044S, N1044I, M1043I, M1043L, M1043T, M1043V, H1047P, H1047I, H1047D, H1047C, H1047L, H1047Q, H1047R, H1047Y, G1049R, and combinations thereof.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletion is selected from the group consisting of E542A, E542G, E542K, E542Q, E542V, E542S, E542R, E542I, E542L, E545A, E545D, E545G, E545K, E545Q, E545V, E545R, E545T, M1043I, M1043L, M1043T,

M1043V, H1047P, H1047I, H1047D, H1047C, H1047L, H1047Q, H1047R, H1047Y, G1049R, and combinations thereof.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletion is selected from the group consisting of E542A, E542G, E542K, E542Q, E542V, E545A, E545D, E545G, E545K, E545Q, M1043I, M1043L, M1043T, M1043V, H1047L, H1047Q, H1047R, H1047Y, G1049R, and combinations thereof. In some embodiments, the PI3K $\alpha$  protein substitution / insertion / deletion is H1047X, where X is any amino acid. In some embodiments, the PI3K $\alpha$  protein substitution / insertion / deletion is H1047R. In some embodiments, the PI3K $\alpha$  protein substitution / insertion / deletion is E542X, where X is any amino acid. In some embodiments, the PI3K $\alpha$  protein substitution / insertion / deletion is E545X, where X is any amino acid. In some embodiments, the PI3K $\alpha$  protein substitution / insertion / deletion is E546X, where X is any amino acid.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletions are selected from H1047R and one of E542A, E542G, E542K, E542Q, E542V, E542S, E542R, E542I, E542L, E545A, E545D, E545G, E545K, E545Q, E545V, E545R, E545T, Q546K, Q546R, Q546P, Q546E, Q546H, E726K, N1044K, N1044Y, N1044S, N1044I, M1043I, M1043L, M1043T, M1043V, H1047P, H1047I, H1047D, H1047C, H1047L, H1047Q, H1047Y, and G1049R.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletions are selected from E726K, H1047P, H1047I, H1047D, H1047C, H1047L, H1047Q, H1047Y, and G1049R. In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletions are selected from Q546K, Q546R, Q546P, Q546E, or Q546H, and E542A, E542G, E542K, E542Q, E542V, E542S, E542R, E542I, and E542L.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletions are selected from E545A, E545D, E545G, E545K, E545Q, E545V, or E545R, and E545T,.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletions are selected from E542A, E542G, E542K, E542Q, E542V, E542S, E542R, E542I, or E542L, and D549N.

In some embodiments, the PI3K $\alpha$  protein substitution/insertion/deletions are selected from E545A, E545D, E545G, E545K, E545Q, E545V, E545R, or E545T, and D453X.

In some embodiments, the cancer (e.g., PI3K $\alpha$ -associated cancer) is selected from a hematological cancer and a solid tumor.

In some embodiments, the cancer is a locally advanced tumor. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is unresectable. In some embodiments, the subject is administered a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, after surgery to resect a tumor (e.g., adjuvant therapy). In some embodiments, the subject is administered a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, prior to surgery to resect a tumor (e.g., neoadjuvant therapy).

In some embodiments, the cancer (e.g., PI3K $\alpha$ -associated cancer) is selected from breast cancer (including both HER2<sup>+</sup> and HER2<sup>-</sup> breast cancer, ER<sup>+</sup> breast cancer, and triple negative breast cancer), endometrial cancer, lung cancer (including non-small cell lung cancer, small cell lung cancer, adenocarcinoma lung cancer, and squamous cell lung carcinoma), esophageal cancer (including esophageal squamous cell carcinoma), ovarian cancer, colorectal cancer, anal cancer, esophagogastric adenocarcinoma, gastric cancer, bladder cancer, goblet cell carcinoma, head and neck cancer (including head and neck squamous cell cancers such as head and neck squamous cell carcinoma and oropharyngeal squamous cell carcinoma), thyroid cancer, glioma, glioblastoma, cervical cancer, lymphangioma, meningioma, melanoma (including uveal melanoma), non-melanoma skin cancer, soft tissue sarcoma, hepatobiliary cancer, prostate cancer, kidney cancer, pancreatic neuroendocrine neoplasms (pNETs), stomach cancer, esophageal cancer, acute myeloid leukemia, myelodysplastic syndrome, B- and T-cell lymphomas, multiple myeloma, relapsed and refractory multiple myeloma, sarcoma, pancreatic cancer, and other CNS cancers (including but not limited to neuromas, adenomas, Schwannomas, astrocytomas, medulloblastomas, and oligodendrogliomas).

In some embodiments, the cancer (e.g., PI3K $\alpha$ -associated cancer) is selected from breast cancer (including both HER2<sup>+</sup> and HER2<sup>-</sup> breast cancer, ER<sup>+</sup> breast cancer, and triple negative breast cancer), colon cancer, rectal cancer, colorectal cancer, ovarian cancer, lymphangioma, meningioma, head and neck squamous cell cancer (HNSCC, including oropharyngeal, nasopharyngeal, and hypopharyngeal squamous cell carcinomas), melanoma (including uveal melanoma), kidney cancer, pancreatic neuroendocrine neoplasms (pNETs), stomach cancer, esophageal cancer, acute myeloid leukemia, relapsed and refractory multiple myeloma, pancreatic

cancer, lung cancer (including adenocarcinoma lung cancer and squamous cell lung carcinoma), and endometrial cancer.

In some embodiments, the cancer (e.g., PI3K $\alpha$ -associated cancer) is selected from breast cancer, lung cancer, endometrial cancer, gastric, esophageal squamous cell carcinoma, ovarian  
5 cancer, colorectal cancer, esophagastic adenocarcinoma, bladder cancer, head and neck cancer, thyroid cancer, glioma, prostate cancer, and cervical cancer.

In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is endometrial cancer. In some embodiments, the cancer is lung cancer.

10 In some embodiments, the cancer is a gynecologic cancer. In some embodiments, the gynecologic cancer is endometrial cancer, ovarian cancer, or cervical cancer.

In some embodiments, the cancer is endometrial cancer. In some embodiments, the endometrial cancer is not deficient in DNA mismatch repair (dMMR), i.e., the endometrial cancer is not dMMR.

15 In some embodiments of any of the methods or uses described herein, the PI3K $\alpha$ -associated cancer is breast cancer.

In some embodiments, the cancer is lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer. In some embodiments, the lung cancer is small cell lung cancer.

In some embodiments, the cancer is esophageal cancer.

20 In some embodiments, the cancer is gastric cancer.

In some embodiments, the cancer is ovarian cancer.

In some embodiments, the cancer is colorectal cancer.

In some embodiments, the cancer is bladder cancer.

In some embodiments, the cancer is head and neck cancer.

25 In some embodiments, the cancer is thyroid cancer.

In some embodiments, the cancer is prostate cancer.

In some embodiments, the cancer is glioma.

In some embodiments, the cancer is cervical cancer.

30 In some embodiments, the cancer is locally advanced. In some embodiments, the cancer is locally advanced breast cancer. In some embodiments, the cancer is locally advanced gynecologic cancer.

In some embodiments, the cancer described herein is a HER2<sup>+</sup> cancer. In some embodiments, the cancer described herein is a HER2<sup>-</sup> cancer.

In some embodiments, the cancer described herein is a HER2-low cancer. In some embodiments, the cancer has a HER2 score (e.g., an IHC score) of 0, +1, or +2. In some  
5       embodiments, the cancer has a HER2 score (e.g., an IHC score) of 0 or +1. In some embodiments, the cancer has a HER2 score of 0. In some embodiments, the cancer has a HER2 score of +1. In some embodiments, the cancer has a HER2 score of +2. In some embodiments, the cancer has a HER2 score of +2 or +3. In some embodiments, the cancer has a HER2 score of +3.

10       In some embodiments, the cancer described herein is a HER2-ultralow cancer (e.g., a cancer with faint, incomplete membrane stained in  $\leq 10\%$  tumor cells tested in an IHC assay).

In some embodiments, the cancer described herein is HER2<sup>+</sup> breast cancer. In some embodiments, the cancer described herein is HER2<sup>-</sup> breast cancer. In some embodiments, the cancer described herein is HER2-low breast cancer.

15       In some embodiments, the cancer described herein is a hormone receptor positive (HR<sup>+</sup>) cancer. In some embodiments, the cancer described herein is a HER2<sup>-</sup> and HR<sup>+</sup> cancer. In some embodiments, the cancer described herein is ER<sup>+</sup>. In some embodiments, the cancer described herein is PR<sup>+</sup>. In some embodiments, the cancer is HR<sup>+</sup>/ER<sup>-</sup> breast cancer.

20       In some embodiments, the cancer described herein is HR<sup>+</sup> and has a HER2 score of 0 or +1. In some embodiments, the cancer described herein is HR<sup>+</sup> and has a HER2 score of 0. In some embodiments, the cancer described herein is HR<sup>+</sup> and has a HER2 score +1.

In some embodiments, the cancer described herein is HR<sup>+</sup> and has a HER2 score of +2 or +3. In some embodiments, the cancer described herein is HR<sup>+</sup> and has a HER2 score of +2. In some embodiments, the cancer described herein is HR<sup>+</sup> and has a HER2 score +3.

25       In some embodiments the subject has been previously identified or determined not to have an activating mutation in AKT, RAS, RAF, or an inactivating mutation or genomic loss of PTEN, or a combination thereof. In some embodiments the subject has been previously identified or determined not to have an activating mutation in AKT and/or PTEN (i.e., inactivation or genomic loss of PTEN). In some embodiments the subject has been previously identified or determined not to have an E17K mutation in AKT. In some embodiments, the PI3K $\alpha$ -associated cancer is selected  
30       from the cancers described in Table 1 and Table 2.

**Table 1. PI3K $\alpha$  Protein Amino Acid Substitutions/Insertions/Deletions<sup>A</sup>**

| <b>Amino Acid Position</b> | <b>Non-Limiting Exemplary Mutations</b>    | <b>Non-Limiting Exemplary PI3K<math>\alpha</math> Associated Cancer(s)</b>                                                                                                                                                                                                                                                                                                                    |
|----------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                          | M1 (Translation Start Site)                | Astrocytoma<br>Glioblastoma Multiforme                                                                                                                                                                                                                                                                                                                                                        |
| 4                          | R4* (Nonsense Mutation)                    | Glioblastoma Multiforme                                                                                                                                                                                                                                                                                                                                                                       |
| 9                          | E9G                                        | Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                        |
| 10                         | L10_M16del                                 | Glioblastoma Multiforme                                                                                                                                                                                                                                                                                                                                                                       |
| 11                         | W11L, W11S, W11_P18del (In Frame Deletion) | Lung Adenocarcinoma,<br>Oligodendroglioma,<br>Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                  |
| 12                         | G12D                                       | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                |
| 13                         | I13T                                       | Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                          |
| 19                         | R19I                                       | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                |
| 27                         | P27T                                       | Hepatocellular Carcinoma                                                                                                                                                                                                                                                                                                                                                                      |
| 36                         | C36Y                                       | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                |
| 38                         | R38C,<br>R38H,<br>R38L,<br>R38S            | Uterine Endometrioid Carcinoma<br>Papillary Renal Cell Carcinoma<br>Papillary Stomach Adenocarcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Glioblastoma Multiforme<br>Cervical Squamous Cell Carcinoma<br>Hepatocellular Carcinoma<br>Uterine Endometrioid Carcinoma<br>Diffuse Type Stomach Adenocarcinoma<br>Lung Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma |
| 39                         | E39G,<br>E39K                              | Uterine Endometrioid Carcinoma<br>Glioblastoma Multiforme                                                                                                                                                                                                                                                                                                                                     |
| 57                         | P57L                                       | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                                            |
| 65                         | E65K                                       | Lung Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                  |
| 66                         | S66C                                       | Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                                                                                                                  |
| 69                         | I69N                                       | Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                          |
| 71                         | V71I                                       | Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                         |
| 75                         | Q75E                                       | Bladder Urothelial Carcinoma<br>Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                              |



|    |                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|----|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    |                                                            | Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 78 | E78* (nonsense mutation)                                   | Lung Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 80 | E80K                                                       | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 81 | E81* (nonsense mutation), E81del (in frame deletion), E81K | Colon Adenocarcinoma<br>Glioblastoma Multiforme<br>Colon Adenocarcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Glioblastoma Multiforme<br>Uterine Endometrioid Carcinoma<br>Lung Squamous Cell Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Breast Invasive Ductal Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                               |
| 83 | F83L, F83S                                                 | Breast Invasive Lobular Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 84 | D84H                                                       | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 86 | T86S                                                       | Hepatocellular Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 87 | R87T                                                       | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 88 | R88Q                                                       | Breast Invasive Ductal Carcinoma<br>Rectal Adenocarcinoma<br>Colon Adenocarcinoma<br>Prostate Adenocarcinoma<br>Cervical Squamous Cell Carcinoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor<br>Tubular Stomach Adenocarcinoma<br>Oligodendroglioma<br>Mucinous Stomach Adenocarcinoma<br>Glioblastoma Multiforme<br>Stomach Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Uterine Mixed Endometrial Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Breast Invasive Lobular Carcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Bladder Urothelial Carcinoma |

|     |                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 90  | C90G, C90R,<br>C90Y                                                                                                 | Glioblastoma Multiforme<br>Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 93  | R93P, R93Q,<br>R93W                                                                                                 | Mucinous Adenocarcinoma of the Colon and Rectum<br>Stomach Adenocarcinoma<br>Glioblastoma Multiforme<br>Uterine Endometrioid Carcinoma<br>Tubular Stomach Adenocarcinoma<br>Mucinous Stomach Adenocarcinoma<br>Bladder Urothelial Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Colon Adenocarcinoma                                                                                                                                                                       |
| 102 | I102del                                                                                                             | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 103 | E103G,<br>E103_G106delins<br>D (In Frame<br>Deletion),<br>E103_P104del (In<br>Frame Deletion)                       | Glioblastoma Multiforme<br>Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 104 | P104L, P104R,<br>P104T                                                                                              | Breast Invasive Ductal Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Lung Adenocarcinoma<br>Colon Adenocarcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma                                                                                                                                                                                                                                                                                    |
| 105 | V105del,<br>V105_R108del                                                                                            | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                            |
| 106 | G106D, G106R,<br>G106S, G106V,<br>G106_R108del<br>(In Frame<br>Deletion),<br>G106_N107del<br>(In Frame<br>Deletion) | Uterine Mixed Endometrial Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Mucinous Carcinoma<br>Oligodendroglioma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Uterine Endometrioid Carcinoma<br>Rectal Adenocarcinoma<br>Lung Squamous Cell Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Tubular Stomach Adenocarcinoma |

|     |                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|     |                                                                            | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 107 | N107S                                                                      | Uterine Endometrioid Carcinoma<br>Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                               |
| 108 | R108C, R108H,<br>R108L                                                     | Prostate Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Glioblastoma Multiforme<br>Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Tubular Stomach Adenocarcinoma<br>Colon Adenocarcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Uterine Mixed Endometrial Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Lung Squamous Cell Carcinoma |
| 109 | E109_I112delins<br>D (In Frame<br>Deletion)                                | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 110 | E110del                                                                    | Uterine Endometrioid Carcinoma<br>Oligodendroglioma<br>Breast Invasive Lobular Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Uterine Mixed Endometrial Carcinoma<br>Colon Adenocarcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Lung Adenocarcinoma<br>Papillary Thyroid Cancer                                                                                                                                                             |
| 111 | K111del, K111E,<br>K111N, K111R,<br>K111_L113del<br>(In Frame<br>Deletion) | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Oligodendroglioma<br>Head and Neck Squamous Cell Carcinoma<br>Colon Adenocarcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Stomach Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Lung Adenocarcinoma<br>Esophageal Adenocarcinoma<br>Lung Squamous Cell Carcinoma<br>Glioblastoma Multiforme                                                                       |

|     |              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 113 | L113del      | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 115 | R115L, R115P | Serous Ovarian Cancer<br>Bladder Urothelial Carcinoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor<br>Uterine Endometrioid Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Rectal Adenocarcinoma<br>Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                    |
| 116 | E116K        | Rectal Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 118 | G118D        | Glioblastoma Multiforme<br>Breast Invasive Ductal Carcinoma<br>Uterine Endometrioid Carcinoma<br>Bladder Urothelial Carcinoma<br>Oligodendroglioma<br>Esophageal Adenocarcinoma<br>Astrocytoma<br>Lung Squamous Cell Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Mucinous Carcinoma<br>Uterine Mixed Endometrial Carcinoma<br>Stomach Adenocarcinoma<br>Pancreatic Adenocarcinoma<br>Papillary Thyroid Cancer<br>Rectal Adenocarcinoma |
| 123 | M123I        | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 124 | P124A        | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 151 | V151M        | Bladder Urothelial Carcinoma<br>Astrocytoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 165 | Y165H        | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 170 | N170S        | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 182 | Y182H        | Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 213 | H213N        | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 224 | A224S        | Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 239 | L239R        | Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 258 | D258N        | Rectal Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 262 | L262I        | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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| 266 | P266T                             | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 267 | L267M                             | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 272 | Y272* (Nonsense Mutation)         | Renal Clear Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 274 | R274K                             | Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 279 | L279I                             | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 282 | M282V                             | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 292 | S292I                             | Glioblastoma Multiforme                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 296 | Q296E                             | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 300 | D300V                             | Lung Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 310 | R310C                             | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 322 | T322A                             | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 335 | R335G                             | Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 337 | K337N                             | Rectal Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 339 | L339I                             | Cervical Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                       |
| 342 | T342S                             | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 344 | V344A, V344G, V344M               | Uterine Endometrioid Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Colon Adenocarcinoma<br>Cervical Squamous Cell Carcinoma<br>Rectal Adenocarcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Uterine Mixed Endometrial Carcinoma<br>Glioblastoma Multiforme                                                                                                                                     |
| 345 | N345H, N345I, N345K, N345T, N345Y | Breast Invasive Lobular Carcinoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Uterine Endometrioid Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Lung Adenocarcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Bladder Urothelial Carcinoma<br>Colon Adenocarcinoma<br>Leiomyosarcoma<br>Glioblastoma Multiforme<br>Uterine Endometrioid Carcinoma |

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|     |                        | Seminoma<br>Tubular Stomach Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Stomach Adenocarcinoma<br>Diffuse Type Stomach Adenocarcinoma<br>Prostate Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Oligodendroglioma |
| 350 | D350G, D350N           | Lung Squamous Cell Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Uterine Endometrioid Carcinoma<br>Colon Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Mucinous Stomach Adenocarcinoma<br>Lung Adenocarcinoma<br>Breast Invasive Lobular Carcinoma                  |
| 351 | I351T                  | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                               |
| 357 | R357Q                  | Uterine Endometrioid Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Colon Adenocarcinoma                                                                                                                                                                    |
| 359 | G359R                  | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                               |
| 363 | G363A                  | Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                        |
| 364 | G364R                  | Uterine Mixed Endometrial Carcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Colon Adenocarcinoma                                                                                                                                                                        |
| 365 | E365K, E365V           | Uterine Endometrioid Carcinoma<br>Bladder Urothelial Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Diffuse Type Stomach Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Head and Neck Squamous Cell Carcinoma                                        |
| 366 | P366R                  | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                             |
| 378 | C378F, C378R,<br>C378Y | Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Uterine Endometrioid Carcinoma<br>Oligodendroglioma                                                                                                                                                        |
| 379 | S379T                  | Cutaneous Melanoma                                                                                                                                                                                                                                                           |

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| 380 | N380S                                          | Diffuse Type Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                            |
| 390 | D390N                                          | Lung Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                            |
| 392 | Y392H                                          | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                 |
| 398 | R398H                                          | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                               |
| 399 | A399T                                          | Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                               |
| 401 | R401Q                                          | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                 |
| 405 | S405F                                          | Intestinal Type Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                         |
| 406 | I406V                                          | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                            |
| 412 | R412Q                                          | Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                         |
| 417 | E417K                                          | Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                   |
| 418 | E418K                                          | Uterine Endometrioid Carcinoma<br>Rectal Adenocarcinoma<br>Mucinous Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                         |
| 420 | C420R                                          | Uterine Endometrioid Carcinoma<br>Tubular Stomach Adenocarcinoma<br>Lung Squamous Cell Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Colon Adenocarcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Stomach Adenocarcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Astrocytoma<br>Cervical Squamous Cell Carcinoma |
| 432 | Y432C                                          | Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                               |
| 447 | P447_L455del (In frame Deletion)               | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                               |
| 449 | P449L, P449S                                   | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                 |
| 450 | H450_P458del (In Frame Deletion)               | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                               |
| 451 | G451R, G451V, G451_D454del (In Frame Deletion) | Head and Neck Squamous Cell Carcinoma<br>Bladder Urothelial Carcinoma<br>Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                  |

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| 452 | L452_G460del<br>(In Frame<br>Deletion)                                                      | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 453 | E453del, E453K,<br>E453Q,<br>E453_G460delins<br>DDF (in Frame<br>Deletion),<br>E453_L455del | Oligodendroglioma<br>Uterine Mixed Endometrial Carcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Astrocytoma<br>Stomach Adenocarcinoma<br>Bladder Urothelial Carcinoma<br>Lung Squamous Cell Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Lung Adenocarcinoma<br>Mucinous Carcinoma<br>Uterine Endometrioid Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Glioblastoma Multiforme<br>Colon Adenocarcinoma |
| 454 | D454Y                                                                                       | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 455 | L455_G463del<br>(In Frame<br>Deletion)                                                      | Glioblastoma Multiforme                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 463 | G463_N465delins<br>D (In Frame<br>Deletion)                                                 | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 469 | E469A,<br>E469delinsDK<br>(In Frame<br>Insertion)                                           | Rectal Adenocarcinoma<br>Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 471 | P471A, P471L                                                                                | Bladder Urothelial Carcinoma<br>Rectal Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Oligoastrocytoma<br>Hepatocellular Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 474 | E474A                                                                                       | Prostate Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 475 | L475F                                                                                       | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 479 | W479*                                                                                       | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |



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| 495 | H495L, H495Y                            | Lung Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 499 | S499F                                   | Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 519 | R519G                                   | Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 520 | D520V                                   | Breast Invasive Lobular Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 522 | E522A                                   | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 531 | L531V                                   | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 539 | P539R, P539S                            | Breast Invasive Ductal Carcinoma<br>Pancreatic Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Lung Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 542 | E542A, E542G,<br>E542K, E542Q,<br>E542V | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Uterine Endometrioid Carcinoma<br>Colon Adenocarcinoma<br>Prostate Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Endocervical Adenocarcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Prostate Adenocarcinoma<br>Papillary Renal Cell Carcinoma<br>Oligoastrocytoma<br>Hepatocellular Carcinoma<br>Bladder Urothelial Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Diffuse Type Stomach Adenocarcinoma<br>Lung Squamous Cell Carcinoma<br>Signet Ring Cell Carcinoma of the Stomach<br>Head and Neck Squamous Cell Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Mucinous Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Glioblastoma Multiforme<br>Lung Adenocarcinoma |
| 545 | E545A, E545D,<br>E545G, E545K,<br>E545Q | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Uterine Endometrioid Carcinoma<br>Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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|     |                                         | Prostate Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Endocervical Adenocarcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Papillary Renal Cell Carcinoma<br>Oligoastrocytoma<br>Hepatocellular Carcinoma<br>Bladder Urothelial Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Diffuse Type Stomach Adenocarcinoma<br>Lung Squamous Cell Carcinoma<br>Signet Ring Cell Carcinoma of the Stomach<br>Head and Neck Squamous Cell Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Mucinous Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Glioblastoma Multiforme<br>Oligodendroglioma<br>Lung Adenocarcinoma<br>Serous Ovarian Cancer<br>Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor<br>Astrocytoma<br>Rectal Adenocarcinoma<br>Stomach Adenocarcinoma<br>Cutaneous Melanoma<br>Esophageal Squamous Cell Carcinoma<br>Breast Invasive Mixed Mucinous Carcinoma<br>Intrahepatic Cholangiocarcinoma<br>Renal Clear Cell Carcinoma<br>Seminoma<br>Esophageal Adenocarcinoma<br>Tubular Stomach Adenocarcinoma<br>Uterine Mixed Endometrial Carcinoma |
| 546 | Q546E, Q546H,<br>Q546K, Q546P,<br>Q546R | Uterine Endometrioid Carcinoma<br>Rectal Adenocarcinoma<br>Oligodendroglioma<br>Stomach Adenocarcinoma<br>Esophageal Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|     |              | Bladder Urothelial Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Breast Invasive Ductal Carcinoma<br>Colon Adenocarcinoma<br>Glioblastoma Multiforme<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma<br>Astrocytoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor<br>Oligoastrocytoma<br>Breast Invasive Lobular Carcinoma<br>Tubular Stomach Adenocarcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Intestinal Type Stomach Adenocarcinoma |
| 547 | E547D, E547K | Lung Squamous Cell Carcinoma<br>Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 552 | W552C        | Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 569 | L569I        | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Prostate Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 576 | S576Y        | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 581 | A581S        | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 589 | D589N        | Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 600 | E600K, E600V | Uterine Endometrioid Carcinoma<br>Bladder Urothelial Carcinoma<br>Lung Adenocarcinoma<br>Breast Invasive Lobular Carcinoma<br>Papillary Stomach Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 603 | D603H        | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 604 | C604R        | Uterine Endometrioid Carcinoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 606 | Y606C        | Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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| 607 | P607Q                                          | Cutaneous Melanoma                                                                                                                                                                                                                                    |
| 609 | P609H                                          | Colon Adenocarcinoma                                                                                                                                                                                                                                  |
| 614 | F614I                                          | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                      |
| 617 | R617Q, R617W                                   | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                        |
| 617 | R617W                                          | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                        |
| 629 | S629C                                          | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                      |
| 636 | V636L                                          | Bladder Urothelial Carcinoma                                                                                                                                                                                                                          |
| 642 | E642K                                          | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma                                                                                                                                                                                           |
| 643 | Q643H                                          | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                        |
| 658 | L658F                                          | Colon Adenocarcinoma                                                                                                                                                                                                                                  |
| 667 | F667L                                          | Uterine Endometrioid Carcinoma<br>Lung Squamous Cell Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma                                                                                                                         |
| 673 | S673T                                          | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                      |
| 674 | E674* (Nonsense mutation),<br>E674D, E674Q     | Papillary Thyroid Cancer<br>Cutaneous Melanoma<br>Bladder Urothelial Carcinoma                                                                                                                                                                        |
| 682 | Q682K,<br>Q682Rfs*18<br>(Frame Shift Deletion) | Cutaneous Melanoma<br>Glioblastoma Multiforme                                                                                                                                                                                                         |
| 683 | R683M                                          | Cutaneous Melanoma                                                                                                                                                                                                                                    |
| 684 | F684L                                          | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                        |
| 693 | R693H                                          | Cervical Squamous Cell Carcinoma                                                                                                                                                                                                                      |
| 710 | E710Q                                          | Bladder Urothelial Carcinoma                                                                                                                                                                                                                          |
| 711 | K711N                                          | Astrocytoma                                                                                                                                                                                                                                           |
| 722 | E722K                                          | Colon Adenocarcinoma                                                                                                                                                                                                                                  |
| 725 | D725G, D725N                                   | Colon Adenocarcinoma<br>Uterine Endometrioid Carcinoma                                                                                                                                                                                                |
| 726 | E726K                                          | Cervical Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Hepatocellular Carcinoma<br>Lung Adenocarcinoma<br>Esophageal Squamous Cell Carcinoma<br>Esophageal Adenocarcinoma<br>Rectal Adenocarcinoma |

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|     |              | Head and Neck Squamous Cell Carcinoma<br>Lung Squamous Cell Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Bladder Urothelial Carcinoma<br>Colon Adenocarcinoma |
| 729 | K729N        | Cutaneous Melanoma                                                                                                                                                 |
| 732 | M732I        | Colon Adenocarcinoma                                                                                                                                               |
| 737 | E737K        | Cutaneous Melanoma                                                                                                                                                 |
| 741 | R741Q        | Serous Ovarian Cancer                                                                                                                                              |
| 744 | F744I        | Stomach Adenocarcinoma                                                                                                                                             |
| 746 | D746Y        | Cutaneous Melanoma                                                                                                                                                 |
| 749 | Q749H        | Cutaneous Melanoma                                                                                                                                                 |
| 752 | L752V        | Bladder Urothelial Carcinoma                                                                                                                                       |
| 766 | L766F        | Breast Invasive Ductal Carcinoma                                                                                                                                   |
| 770 | R770Q        | Uterine Endometrioid Carcinoma                                                                                                                                     |
| 773 | S773F        | Cutaneous Melanoma                                                                                                                                                 |
| 777 | R777M, R777K | Cutaneous Melanoma<br>Colon Adenocarcinoma                                                                                                                         |
| 791 | E791Q        | Bladder Urothelial Carcinoma                                                                                                                                       |
| 811 | M811I        | Uterine Endometrioid Carcinoma                                                                                                                                     |
| 816 | I816S        | Uterine Endometrioid Carcinoma                                                                                                                                     |
| 818 | R818C, R818H | Cutaneous Melanoma<br>Uterine Endometrioid Carcinoma                                                                                                               |
| 849 | E849K        | Serous Ovarian Cancer                                                                                                                                              |
| 852 | R852Q        | Leiomyosarcoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma                                                                                      |
| 865 | G865D        | Cutaneous Melanoma                                                                                                                                                 |
| 866 | L866F, L866W | Cervical Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma                                                                                                 |
| 879 | Q879R        | Stomach Adenocarcinoma                                                                                                                                             |
| 886 | K886E        | Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous Histiocytoma/High-Grade Spindle Cell Sarcoma                                                                |
| 901 | C901F        | Uterine Endometrioid Carcinoma<br>Astrocytoma<br>Breast Invasive Ductal Carcinoma<br>Head and Neck Squamous Cell Carcinoma                                         |
| 903 | G903E        | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma                                                                                                        |

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| 905  | C905S                        | Head and Neck Squamous Cell Carcinoma                                                                                                                  |
| 909  | F909C                        | Esophageal Adenocarcinoma                                                                                                                              |
| 914  | G914R                        | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Astrocytoma                                                                             |
| 929  | L929M                        | Uterine Endometrioid Carcinoma                                                                                                                         |
| 930  | F930V                        | Uterine Endometrioid Carcinoma                                                                                                                         |
| 939  | D939G                        | Breast Invasive Carcinoma (NOS)<br>Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma                                                  |
| 948  | K948E                        | Intestinal Type Stomach Adenocarcinoma                                                                                                                 |
| 951  | R951C                        | Rectal Adenocarcinoma                                                                                                                                  |
| 953  | P953S                        | Uterine Endometrioid Carcinoma                                                                                                                         |
| 956  | L956F                        | Bladder Urothelial Carcinoma                                                                                                                           |
| 958  | Q958R                        | Uterine Mixed Endometrial Carcinoma                                                                                                                    |
| 970  | E970K                        | Esophageal Squamous Cell Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Colon Adenocarcinoma |
| 971  | C971R                        | Head and Neck Squamous Cell Carcinoma                                                                                                                  |
| 978  | E978K                        | Bladder Urothelial Carcinoma                                                                                                                           |
| 979  | R979G                        | Pancreatic Adenocarcinoma                                                                                                                              |
| 985  | Y985*                        | Pleural Mesothelioma, Biphasic Type                                                                                                                    |
| 989  | L989V                        | Breast Invasive Ductal Carcinoma                                                                                                                       |
| 992  | R992L, R992P                 | Bladder Urothelial Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Mucinous Carcinoma                                      |
| 997  | L997I                        | Uterine Endometrioid Carcinoma                                                                                                                         |
| 1002 | F1002L                       | Uterine Endometrioid Carcinoma                                                                                                                         |
| 1004 | M1004I,<br>M1004R,<br>M1004V | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Bladder Urothelial Carcinoma<br>Lung Squamous Cell Carcinoma                     |
| 1005 | M1005V                       | Oligodendroglioma                                                                                                                                      |
| 1006 | L1006R                       | Uterine Endometrioid Carcinoma                                                                                                                         |
| 1007 | G1007R                       | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Head and Neck Squamous Cell Carcinoma                                            |

|      |                                         |                                                                                                                                                                                                                                                                                                                                                                          |
|------|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                                         | Colon Adenocarcinoma<br>Endocervical Adenocarcinoma                                                                                                                                                                                                                                                                                                                      |
| 1012 | E1012Q                                  | Bladder Urothelial Carcinoma                                                                                                                                                                                                                                                                                                                                             |
| 1015 | S1015Y                                  | Mucinous Adenocarcinoma of the Colon and Rectum                                                                                                                                                                                                                                                                                                                          |
| 1016 | F1016C                                  | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                           |
| 1017 | D1017N                                  | Pancreatic Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                |
| 1020 | A1020T                                  | Uterine Endometrioid Carcinoma                                                                                                                                                                                                                                                                                                                                           |
| 1021 | Y1021C, Y1021H                          | Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor<br>Colon Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma<br>Uterine Endometrioid Carcinoma<br>Stomach Adenocarcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Tubular Stomach Adenocarcinoma                         |
| 1025 | T1025A, T1025S                          | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                             |
| 1023 | R1023Q <sup>†</sup>                     | Colorectal Cancer                                                                                                                                                                                                                                                                                                                                                        |
| 1026 | L1026I                                  | Cutaneous Melanoma                                                                                                                                                                                                                                                                                                                                                       |
| 1029 | D1029H                                  | Uterine Serous Carcinoma/Uterine Papillary Serous<br>Carcinoma                                                                                                                                                                                                                                                                                                           |
| 1037 | E1037K                                  | Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                         |
| 1040 | M1040I, M1040V                          | Head and Neck Squamous Cell Carcinoma<br>Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                |
| 1043 | M1043I,<br>M1043L,<br>M1043T,<br>M1043V | Breast Invasive Lobular Carcinoma<br>Tubular Stomach Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Papillary Thyroid Cancer<br>Esophageal Squamous Cell Carcinoma<br>Colon Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Bladder Urothelial Carcinoma<br>Pancreatic Adenocarcinoma<br>Oligodendroglioma |

|      |                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                                | Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Glioblastoma Multiforme<br>Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 1044 | N1044I, N1044K, N1044Y         | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 1045 | D1045A, D1045V                 | Uterine Endometrioid Carcinoma<br>Lung Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 1047 | H1047L, H1047Q, H1047R, H1047Y | Esophageal Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma<br>Hepatocellular Carcinoma<br>Cutaneous Melanoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Bladder Urothelial Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Intrahepatic Cholangiocarcinoma<br>Uterine Mixed Endometrial Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Renal Clear Cell Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Lung Squamous Cell Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Breast Invasive Carcinoma (NOS)<br>Astrocytoma<br>Colon Adenocarcinoma<br>Leiomyosarcoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor<br>Oligodendroglioma<br>Serous Ovarian Cancer<br>Mucinous Stomach Adenocarcinoma<br>Rectal Adenocarcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Diffuse Type Stomach Adenocarcinoma<br>Prostate Adenocarcinoma<br>Lung Adenocarcinoma<br>Stomach Adenocarcinoma<br>Tubular Stomach Adenocarcinoma |



|      |                                                    |                                                                                                                                                                                                                                         |
|------|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                                                    | Adrenocortical Carcinoma<br>Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous<br>Histiocytoma/High-Grade Spindle Cell Sarcoma<br>Glioblastoma Multiforme<br>Oligoastrocytoma                                                       |
| 1048 | H1048R                                             | Colon Adenocarcinoma<br>Renal Clear Cell Carcinoma                                                                                                                                                                                      |
| 1049 | G1049R                                             | Intestinal Type Stomach Adenocarcinoma<br>Bladder Urothelial Carcinoma<br>Renal Clear Cell Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Uterine Endometrioid Carcinoma<br>Colon Adenocarcinoma |
| 1052 | T1052K                                             | Hepatocellular Carcinoma<br>Colon Adenocarcinoma                                                                                                                                                                                        |
| 1055 | M1055I                                             | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                     |
| 1058 | I1058M                                             | Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor                                                                                                                                                                       |
| 1065 | H1065L                                             | Breast Invasive Lobular Carcinoma                                                                                                                                                                                                       |
| 1066 | A1066V                                             | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                     |
| 1068 | N1068Y,<br>N1068fs*5<br>(Frame Shift<br>Insertion) | Pleural Mesothelioma, Epithelioid Type<br>Dedifferentiated Liposarcoma<br>Head and Neck Squamous Cell Carcinoma                                                                                                                         |
| 1069 | *1069Wext*4<br>(nonstop<br>Mutation)               | Glioblastoma Multiforme                                                                                                                                                                                                                 |

<sup>A</sup> Unless noted otherwise, the mutations of Table 1 are found in cBioPortal database derived from Cerami et al. *The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data*. Cancer Discovery. May 2012 2; 401; and Gao et al. *Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal*. Sci. Signal. 6, pl1 (2013).

† Velho S, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S Jr, Duval A, Carneiro F, Machado JC, Hamelin R, Seruca R. The prevalence of PIK3CA mutations in gastric and colon cancer. Eur J Cancer. 2005 Jul;41(11):1649-54. doi: 10.1016/j.ejca.2005.04.022. PMID: 15994075.

**Table 2. Additional PI3K $\alpha$  Protein Amino Acid Substitutions/Insertions/Deletions<sup>A</sup>**

| <b>Amino Acid Position</b> | <b>Non-Limiting Exemplary Mutations</b> | <b>Non-Limiting Exemplary PI3K<math>\alpha</math> Associated Cancer(s)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1043                       | M1043I,<br>M1043L,<br>M1043T,<br>M1043V | Breast Invasive Lobular Carcinoma<br>Tubular Stomach Adenocarcinoma<br>Uterine Endometrioid Carcinoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Papillary Thyroid Cancer<br>Esophageal Squamous Cell Carcinoma<br>Colon Adenocarcinoma<br>Breast Invasive Ductal Carcinoma<br>Bladder Urothelial Carcinoma<br>Pancreatic Adenocarcinoma<br>Oligodendroglioma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Glioblastoma Multiforme<br>Head and Neck Squamous Cell Carcinoma                                                                                               |
| 1044                       | N1044I, N1044K,<br>N1044Y               | Uterine Endometrioid Carcinoma<br>Breast Invasive Ductal Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 1045                       | D1045A,<br>D1045V                       | Uterine Endometrioid Carcinoma<br>Lung Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 1047                       | H1047L,<br>H1047Q,<br>H1047R, H1047Y    | Esophageal Squamous Cell Carcinoma<br>Uterine Endometrioid Carcinoma<br>Hepatocellular Carcinoma<br>Cutaneous Melanoma<br>Mucinous Adenocarcinoma of the Colon and Rectum<br>Bladder Urothelial Carcinoma<br>Cervical Squamous Cell Carcinoma<br>Intrahepatic Cholangiocarcinoma<br>Uterine Mixed Endometrial Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Renal Clear Cell Carcinoma<br>Uterine Serous Carcinoma/Uterine Papillary Serous Carcinoma<br>Head and Neck Squamous Cell Carcinoma<br>Lung Squamous Cell Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Breast Invasive Carcinoma (NOS) |

|      |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------|----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|      |                                                    | Astrocytoma<br>Colon Adenocarcinoma<br>Leiomyosarcoma<br>Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor<br>Oligodendroglioma<br>Serous Ovarian Cancer<br>Mucinous Stomach Adenocarcinoma<br>Rectal Adenocarcinoma<br>Intestinal Type Stomach Adenocarcinoma<br>Diffuse Type Stomach Adenocarcinoma<br>Prostate Adenocarcinoma<br>Lung Adenocarcinoma<br>Stomach Adenocarcinoma<br>Tubular Stomach Adenocarcinoma<br>Adrenocortical Carcinoma<br>Undifferentiated Pleomorphic Sarcoma/Malignant Fibrous<br>Histiocytoma/High-Grade Spindle Cell Sarcoma<br>Glioblastoma Multiforme<br>Oligoastrocytoma |
| 1048 | H1048R                                             | Colon Adenocarcinoma<br>Renal Clear Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 1049 | G1049R                                             | Intestinal Type Stomach Adenocarcinoma<br>Bladder Urothelial Carcinoma<br>Renal Clear Cell Carcinoma<br>Breast Invasive Ductal Carcinoma<br>Breast Invasive Lobular Carcinoma<br>Uterine Endometrioid Carcinoma<br>Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                  |
| 1052 | T1052K                                             | Hepatocellular Carcinoma<br>Colon Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 1055 | M1055I                                             | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1058 | I1058M                                             | Uterine Carcinosarcoma/Uterine Malignant Mixed<br>Mullerian Tumor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 1065 | H1065L                                             | Breast Invasive Lobular Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 1066 | A1066V                                             | Uterine Mixed Endometrial Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1068 | N1068Y,<br>N1068fs*5<br>(Frame Shift<br>Insertion) | Pleural Mesothelioma, Epithelioid Type<br>Dedifferentiated Liposarcoma<br>Head and Neck Squamous Cell Carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

<sup>A</sup> Unless noted otherwise, the mutations of Table 2 are found in cBioPortal database derived from Cerami et al. *The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data*. Cancer Discovery. May 2012 2; 401; and Gao et al. *Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal*. Sci. Signal. 6, pl1 (2013).

<sup>†</sup> Velho S, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S Jr, Duval A, Carneiro F, Machado JC, Hamelin R, Seruca R. The prevalence of PIK3CA mutations in gastric and colon cancer. *Eur J Cancer*. 2005 Jul;41(11):1649-54. doi: 10.1016/j.ejca.2005.04.022. PMID: 15994075.

In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, includes a splice variation in a PI3K $\alpha$  mRNA which results in an expressed protein that is an alternatively spliced variant of PI3K $\alpha$  having at least one residue deleted (as compared to the wild type PI3K $\alpha$  protein) resulting in a constitutive activity of a PI3K $\alpha$  protein domain.

In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, includes at least one point mutation in a *PIK3CA* gene that results in the production of a PI3K $\alpha$  protein that has one or more amino acid substitutions or insertions or deletions in a *PIK3CA* gene that results in the production of a PI3K $\alpha$  protein that has one or more amino acids inserted or removed, as compared to the wild type PI3K $\alpha$  protein. In some cases, the resulting mutant PI3K $\alpha$  protein has increased activity, as compared to a wild type PI3K $\alpha$  protein or a PI3K $\alpha$  protein not including the same mutation. In some embodiments, the compounds described herein selectively inhibit the resulting mutant PI3K $\alpha$  protein relative to a wild type PI3K $\alpha$  protein or a PI3K $\alpha$  protein not including the same mutation.

Exemplary Sequence of Human Phosphatidylinositol 4,5-bisphosphate 3-kinase isoform alpha (UniProtKB entry P42336) (SEQ ID NO: 1)

MPPRPSSGEL WGIHLMPPRI LVECLLPNGM IVTLECLREA TLITIKHELF KEARKYPLHQ  
LLQDESSYIF VSVTQEAERE EFFDETRRLC DLRLFQPFLL  
VIEPVGNREE KILNREIGFA IGMPVCEFDK VKDPEVQDFR RNILNVCKEA  
VDLRDLNSPH SRAMYVYPPN VESSPELPKH IYNKLDKGQI IVVIWVIVSP  
NNDKQKYTLK INHDCVPEQV IAEAIRKKTR SMLLSSEQLK LCVLEYQGKY  
ILKVCGCDEY FLEKYPLSQY KYIRSCIMLG RMPNLMLMAK ESLYSQLPMD  
CFTMPYSYRR ISTATPYMNG ETSTKSLWVI NSALRIKILC ATYVNVNIRD  
IDKIYVRTGI YHGGEPLCDN VNTQRVPCSN PRWNEWLNVD IYIPDLPRAA

RLCLSICSVK GRKGAKKEHC PLAWGNINLF DYTDTLVSGK MALNLWPVPH  
 GLEDLLNPIG VTGSNPKNKET PCLELEFDWF SSVVKFPDMS VIEEHANWSV  
 SREAGFSYSH AGLSNRLARD NELRENDKEQ LKAISTRDPL SEITEQEKDF  
 LWSHRHYCVT IPEILPKLLL SVKWNSRDEV AQMYCLVKDW PPIKPEQAME  
 5 LLDCNYPDPM VRGFAVRCLE KYLTDDKLSQ YLIQLVQVLK YEQYLDNLLV  
 RFLKKALTN QRIGHFFFWH LKSEMHNKTV SQRFGLLLES YCRACGMYLK  
 HLNQRQEAME KLINLTDILK QEKKDETQKV QMKFLVEQMR RPDFMDALQG  
 FLSPLNPAHQ LGNLRLEECR IMSSAKRPLW LNWENPDIMS ELLFQNNII  
 FKNGDDLQD MLTLQIIRIM ENIWQNQGLD LRMLPYGCLS IGDCVGLIEV  
 10 VRNSHTIMQI QCKGGLKGAL QFNSHTLHQW LKDKNKGEIY DAAIDLFTRS  
 CAGYCVATFI LGIGDRHNSN IMVKDDGQLF HIDFGHFLDH KKKKFGYKRE  
 RVPFVLTQDF LIVISKGAQE CTKTREFERF QEMCYKAYLA IRQHANLFIN  
 LFSMMLGSGM PELQSFDIA YIRKTLALDK TEQEALYFM KQMNDAAHHGG  
 WTTKMDWIFH TIKQHALN

15

In some embodiments, 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable thereof, is useful for treating a cancer that has been identified as having one or more PI3K $\alpha$  mutations. Accordingly, provided herein are methods for treating a subject diagnosed with (or identified as
 20 having) a cancer that include administering to the subject a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

Also provided herein are methods for treating a subject identified or diagnosed as having a PI3K $\alpha$ -associated cancer that include administering to the subject a therapeutically effective
 25 amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof. In some embodiments, the subject that has been identified or diagnosed as having a PI3K $\alpha$ -associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein,
 30 or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some

embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is an PI3K $\alpha$ -associated cancer.

In some embodiments, the crystalline forms of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof described herein, are capable of crossing the blood-brain barrier (BBB) and inhibiting mutant PI3K $\alpha$  in the brain and/or other central nervous system (CNS) structures after administration to a subject. In some embodiments, the crystalline forms of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof described herein, are capable of crossing the BBB in a therapeutically effective amount after administration to a subject.

The term “regulatory agency” refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

Also provided are methods for treating cancer in a subject in need thereof, the method comprising: (a) detecting a PI3K $\alpha$ -associated cancer in the subject; and (b) administering to the subject a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., an immunotherapy). In some embodiments, the subject was previously treated with another anticancer treatment, e.g., at least partial resection of the tumor or radiation therapy. In some embodiments, the subject is determined to have a PI3K $\alpha$ -associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is an PI3K $\alpha$ -associated cancer.

Also provided are methods of treating a subject that include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, and administering (e.g., specifically or selectively administering) a therapeutically effective amount of

1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof, to the subject determined to have a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same. Some  
5   embodiments of these methods further include administering to the subject another anticancer agent (e.g., an immunotherapy). In some embodiments of these methods, the subject was previously treated with another anticancer treatment, e.g., at least partial resection of a tumor or radiation therapy. In some embodiments, the subject is a subject suspected of having a PI3K $\alpha$ -associated cancer, a subject presenting with one or more symptoms of a PI3K $\alpha$ -associated cancer,  
10   or a subject having an elevated risk of developing a PI3K $\alpha$ -associated cancer. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. Additional, non-limiting assays that may be used in these methods are described  
15   herein. Additional assays are also known in the art.

Also provided is 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof, for use in treating a PI3K $\alpha$ -associated cancer in a subject identified or diagnosed as having a PI3K $\alpha$ -associated cancer through a step of performing an assay  
20   (e.g., an *in vitro* assay) on a sample obtained from the subject to determine whether the subject has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, where the presence of a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, identifies that the subject has a PI3K $\alpha$ -associated cancer. Also provided is the use of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-  
25   2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, for the manufacture of a medicament for treating a PI3K $\alpha$ -associated cancer in a subject identified or diagnosed as having a PI3K $\alpha$ -associated cancer through a step of performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a *PIK3CA* gene,  
30   a PI3K $\alpha$  protein, or expression or activity or level of any of the same where the presence of dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, identifies that the subject has a PI3K $\alpha$ -associated cancer. Some embodiments described

herein further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject is determined to have a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, through the performance of the assay, should be administered 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy.

Also provided is 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the treatment of a cancer in a subject in need thereof, or a subject identified or diagnosed as having a PI3K $\alpha$ -associated cancer. Also provided is the use of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, for the manufacture of a medicament for treating a cancer in a subject identified or diagnosed as having a PI3K $\alpha$ -associated cancer. In some embodiments, a subject is identified or diagnosed as having a PI3K $\alpha$ -associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject. As provided herein, a PI3K $\alpha$ -associated cancer includes those described herein and known in the art.

In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same. In some embodiments, the subject has a tumor that is positive for a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same. In some embodiments, the subject can be a subject with a tumor(s) that is positive for a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same. In some embodiments, the subject can be a subject whose tumors have a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same. In some embodiments, the subject is suspected of having a PI3K $\alpha$ -associated cancer. In some embodiments, provided herein are methods for treating a PI3K $\alpha$ -associated cancer in a subject in need of such treatment, the



method comprising a) detecting a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same in a sample from the subject; and b) administering a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same includes one or more PI3K $\alpha$  protein point mutations/insertions/deletions. Non-limiting examples of PI3K $\alpha$  protein point mutations/insertions/deletions are described in Table 1 and Table 2. In some embodiments, the PI3K $\alpha$  protein point mutation/insertion/deletion is H1047X, where X is any amino acid. In some  
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embodiments, the PI3K $\alpha$  protein point mutations/insertions/deletions are selected from the group consisting of E542A, E542G, E542K, E542Q, E542V, E545A, E545D, E545G, E545K, E545Q, M1043I, M1043L, M1043T, M1043V, H1047L, H1047Q, H1047R, H1047Y, and G1049R. In some embodiments, the cancer with a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the tumor with a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit.

In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same. Also provided are methods of treating a subject that include administering a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, to a subject having a clinical record that indicates that the subject has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the  
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same.

In some embodiments, the methods provided herein include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or level of any of the same. In some such  
30  
embodiments, the method also includes administering to a subject determined to have a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-

methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the method includes determining that a subject has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or level of any of the same via an assay performed on a sample obtained from the subject. In such embodiments, the method also includes administering to a subject a therapeutically effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the dysregulation in a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same is one or more point mutation in the *PIK3CA* gene (e.g., any of the one or more of the PI3K $\alpha$  point mutations described herein). The one or more point mutations in a *PIK3CA* gene can result, e.g., in the translation of a PI3K $\alpha$  protein having one or more of the following amino acid substitutions, deletions, and insertions: E542A, E542G, E542K, E542Q, E542V, E545A, E545D, E545G, E545K, E545Q, M1043I, M1043L, M1043T, M1043V, H1047L, H1047Q, H1047R, H1047Y, and G1049R. The one or more mutations in a *PIK3CA* gene can result, e.g., in the translation of an PI3K $\alpha$  protein having one or more of the following amino acids: 542, 545, 1043, and 1047 and 1049. In some embodiments, the dysregulation in a *PIK3CA* gene, a PI3K $\alpha$  protein protein, or expression or activity or level of any of the same is one or more PI3K $\alpha$  amino acid substitutions (e.g., any of the PI3K $\alpha$  amino acid substitution described herein). Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., an immunotherapy).

In some embodiments, an assay used to determine whether the subject has a dysregulation of a *PIK3CA* gene, or a PI3K $\alpha$  protein, or expression or activity or level of any of the same, using a sample from a subject can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labeled nucleic acid probe or at least one labeled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or levels of any of the same (see, e.g., the references cited herein). In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the subject. In some embodiments, the subject is a subject suspected of having a PI3K $\alpha$  -associated cancer, a

subject having one or more symptoms of a PI3K $\alpha$ -associated cancer, and/or a subject that has an increased risk of developing a PI3K $\alpha$ -associated cancer).

In some embodiments, dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). See, e.g., Karachaliou et al., *Ann. Transl. Med.*, 3(3):36, 2016. Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments, cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or the expression or activity or level of any of the same.

In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a monotherapy at a dose of about 10 mg to about 200 mg per day, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, or about 200 mg.

In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt

and/or solvate thereof, is administered to a subject as a monotherapy at a dose of about 20 mg to about 200 mg per day, for example, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, or about 200 mg.

5 In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a monotherapy at a dose of about 20 mg to about 160 mg per day, for example, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, or about 160 mg.

10 In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a monotherapy at a dose of about 60 mg to about 160 mg per day, for example, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, or about 160 mg.

15 In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject once per day. In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject orally.

20 Also provided are methods of treating a PI3K $\alpha$ -associated cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the crystalline Form 1 of Compound A, or a pharmaceutical composition comprising same.

25 Also provided are methods for treating breast cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the crystalline Form 1 of Compound A, or a pharmaceutical composition comprising same.

Also provided are methods for treating gynecologic cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the crystalline Form 1 of Compound A, or a pharmaceutical composition comprising same.

30 Also provided are methods for treating endometrial cancer in a subject in need thereof the method comprising administering to the subject a therapeutically effective amount of the crystalline Form 1 of Compound A, or a pharmaceutical composition comprising same.

### Other Methods

Also provided is a method for inhibiting PI3K $\alpha$  activity in a cell, comprising contacting the cell with 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof. In some  
5       embodiments, the contacting is *in vitro*. In some embodiments, the contacting is *in vivo*. In some  
embodiments, the contacting is *in vivo*, wherein the method comprises administering an effective  
amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-  
trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, to a subject having  
10       a cell having aberrant PI3K $\alpha$  activity. In some embodiments, the cell is a cancer cell. In some  
embodiments, the cancer cell is any cancer as described herein. In some embodiments, the cancer  
cell is a PI3K $\alpha$ -associated cancer cell. As used herein, the term "contacting" refers to the bringing  
together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting"  
a PI3K $\alpha$  protein with a compound provided herein includes the administration of a compound  
15       provided herein to a subject, such as a human, having a PI3K $\alpha$  protein, as well as, for example,  
introducing a compound provided herein into a sample containing a cellular or purified preparation  
containing the PI3K $\alpha$  protein.

Also provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, the  
method comprising contacting a cell with an effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-  
20       (5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically  
acceptable salt and/or solvate thereof, or a pharmaceutical composition thereof as defined herein.

Further provided herein is a method of increasing cell death, *in vitro* or *in vivo*, the method  
comprising contacting a cell with an effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-  
difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt  
25       and/or solvate thereof, or a pharmaceutical composition thereof as defined herein. Also provided  
herein is a method of increasing tumor cell death in a subject. The method comprises administering  
to the subject an effective amount of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-  
methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or  
solvate thereof, in an amount effective to increase tumor cell death.

30       When employed as pharmaceuticals, 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-  
methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, including pharmaceutically acceptable salts

and/or solvates thereof, can be administered in the form of pharmaceutical compositions as described herein.

### *Combinations*

5           Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more independently selected additional therapeutic agents.

10           Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a combination therapy comprising a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more independently selected additional therapeutic agents.

15           The other component(s) of such conjoint treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, such as other kinase inhibitors, signal transduction inhibitors and/or monoclonal antibodies. Surgery can be open surgery or minimally invasive surgery, and includes partial and total resection of a solid tumor.

20           1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salts and/or solvates thereof, therefore may also be useful as an adjuvant to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example, a chemotherapeutic agent that works by the same or by a different mechanism of action. In some embodiments, 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, can be used prior to administration of an additional therapeutic agent or additional therapy. For example, a subject in need thereof can be administered one or more doses of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, for a period of time and then undergo at least partial resection of the tumor. In  
30           some embodiments, the treatment with one or more doses of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt

and/or solvate thereof, reduces the size of the tumor (e.g., the tumor burden) prior to the at least partial resection of the tumor. In some embodiments, a subject in need thereof can be administered one or more doses of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, for a period of time and under one or more rounds of radiation therapy. In some embodiments, the treatment with one or more doses of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, reduces the size of the tumor (e.g., the tumor burden) prior to the one or more rounds of radiation therapy.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising:

(a) testing or having tested a subject to determine that the subject has a PI3K $\alpha$ -associated cancer, and

(b) administering to the subject a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising:

(a) determining that the subject has a PI3K $\alpha$ -associated cancer; and

(b) administering to the subject a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising:

(a) determining that the subject has a PI3K $\alpha$ -associated cancer; and

(b) administering to the subject a combination therapy comprising a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject previously determined to have a PI3K $\alpha$ -associated cancer, comprising administering to the subject a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject previously determined to have a PI3K $\alpha$ -associated cancer, comprising administering to the subject of a combination therapy comprising a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one or more additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject

(a) a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and

(b) one or more independently selected additional therapeutic agents selected from the group consisting of: a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, and a RAF inhibitor, a PIM (e.g., PIM1 and PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional therapeutic agent. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a combination therapy comprising:



(a) a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and

5 (b) one or more independently selected additional therapeutic agents selected from the group consisting of: a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, and a RAF inhibitor, a PIM (e.g., PIM1 and PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments, a crystalline  
10 form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional therapeutic agent. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently  
15 selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising:

(a) testing or having tested a subject to determine that the subject has a PI3K $\alpha$ -associated cancer, and

20 (b) administering to the subject a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an  
25 EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, a RAF inhibitor, a PIM (e.g., PIM1 and PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional therapeutic agent. In some embodiments, a  
30 crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-

2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising:

- 5 (a) determining that the subject has a PI3K $\alpha$ -associated cancer; and
- (b) administering to the subject a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, a RAF inhibitor, a PIM (e.g., PIM1 and PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional therapeutic agent. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently selected additional therapeutic agents.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising:

- 20 (a) determining that the subject has a PI3K $\alpha$ -associated cancer; and
- (b) administering to the subject a combination therapy comprising a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, a RAF inhibitor, a PIM (e.g., PIM1 and PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional

therapeutic agent. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently selected additional therapeutic agents.

5           Some embodiments provide a method of treating cancer in a subject previously determined to have a PI3K $\alpha$ -associated cancer, comprising administering to the subject

(a) a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and

10           (b) one or more independently selected additional therapeutic agents selected from the group consisting of: a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, and a RAF inhibitor, a PIM (e.g., PIM1  
15 and PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional therapeutic agent. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a  
20 pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently selected additional therapeutic agents.

          Some embodiments provide a method of treating cancer in a subject previously determined to have a PI3K $\alpha$ -associated cancer, comprising administering to the subject of a combination therapy comprising a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or  
25 solvate thereof, and a selective estrogen receptor modulator (SERM) / selective estrogen receptor degrader (SERD), a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, an EGFR inhibitor, an immune checkpoint inhibitor, a MEK inhibitor, a RAS inhibitor, a RAF inhibitor, a PIM (e.g., PIM1 and  
30 PIM3) inhibitor, or a combination of any of the foregoing. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-

trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with one additional therapeutic agent. In some embodiments, a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered with two independently selected additional therapeutic agents.

In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to standard therapy (e.g., administration of a chemotherapeutic agent, such as a multi-kinase inhibitor, immunotherapy, or radiation (e.g., radioactive iodine)). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to prior therapy (e.g., administration of a chemotherapeutic agent, such as a multi-kinase inhibitor, immunotherapy, or radiation (e.g., radioactive iodine)). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that has no standard therapy. In some embodiments, a subject is PI3K $\alpha$  inhibitor naïve. For example, the subject is naïve to treatment with a selective PI3K $\alpha$  inhibitor. In some embodiments, a subject is not PI3K $\alpha$  inhibitor naïve. In some embodiments, a subject is kinase inhibitor naïve. In some embodiments, a subject is not kinase inhibitor naïve. In some embodiments, a subject has undergone prior therapy, for example, treatment with any one of the additional therapeutic agents described herein, or a combination thereof. In some embodiments, the subject has undergone prior therapy with a multi-kinase inhibitor (MKI) or another PI3K $\alpha$  inhibitor, such as buparlisib (BKM120), alpelisib (BYL719), RLY-2608, WX-037, idelalisib, duvelisib, copanlisib, umbralisib, (ALIQOPATM, BAY80-6946), dactolisib (NVP-BEZ235, BEZ-235), taselisib (GDC-0032, RG7604), sonolisib (PX-866), fimepinostat (CUDC-907), bimiralisib (PQR309), ZSTK474, SF1126, AZD8835, inavolisib (GDC-0077), ASN003, pictilisib (GDC-0941), pilaralisib (XL147, SAR245408), gedatolisib (PF-05212384, PKI-587), serabelisib (TAK-117, MLN1117, INK 1117), BGT-226 (NVP-BGT226), PF-04691502, apitolisib (GDC-0980), omipalisib (GSK2126458, GSK458), voxtalisib (XL756, SAR245409), AMG 511, CH5132799, GSK1059615, paxalisib (GDC-0084, RG7666), VS-5584 (SB2343), PKI-402, wortmannin, LY294002, PI-103, rigosertib (ON-01910 sodium salt), voxtalisib (XL-765), LY2023414, SAR260301, KIN-193 (AZD-6428), acalisib (GS-9820), AMG319, or GSK2636771.

In some embodiments, the subject was previously administered one or more PI3K $\alpha$  inhibitors. In some embodiments, the subject was previously administered alpelisib (BYL719), RLY-2608, or both alpelisib (BYL719) and RLY-2608.

5 In some embodiments of any the methods described herein a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents. In some embodiments, the therapeutically effective amount of the additional therapeutic agent(s) is the therapeutically effective amount of the agent(s) when administered as a monotherapy. In some embodiments, the therapeutically effective amount of the additional therapeutic agent(s) is the amount administered in combination with a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein.

15 In some embodiments, the subject is also instructed to maintain a particular diet and/or exercise regimen to control blood sugar levels.

Accordingly, also provided herein is a method of treating cancer, comprising administering to a subject in need thereof a pharmaceutical combination for treating cancer which comprises (a) a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the crystalline form 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea and the additional therapeutic agent are together effective in treating the cancer.

25 In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity, or level of any of the same.

30 These additional therapeutic agents may be administered with one or more doses of a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, or

pharmaceutical composition thereof, as part of the same or separate dosage forms, via the same or different routes of administration, and/or on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

Also provided herein is (i) a pharmaceutical combination for treating a cancer in a subject  
5 in need thereof, which comprises (a) a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein or known in the art), and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment  
10 of cancer, wherein the amounts of a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salt and/or solvate thereof, and of the additional therapeutic agent are together effective in treating the cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial  
15 package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer in a subject in need thereof. In some embodiments, the cancer is a PI3K $\alpha$ -associated cancer.

The term “pharmaceutical combination”, as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed  
20 and non-fixed combinations of the active ingredients. The term “fixed combination” means that a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and at least one additional therapeutic agent (e.g., a chemotherapeutic agent), are both administered to a subject simultaneously in the form of a single composition or dosage. The term “non-fixed  
25 combination” means that a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and at least one additional therapeutic agent (e.g., chemotherapeutic agent) are formulated as separate compositions or dosages such that they may be administered to a subject in need thereof simultaneously, concurrently or sequentially with variable intervening time limits,  
30 wherein such administration provides effective levels of the two or more compounds in the body

of the subject. These also apply to cocktail therapies, e.g., the administration of three or more active ingredients.

Accordingly, also provided herein is a method of treating a cancer, comprising administering to a subject in need thereof a pharmaceutical combination for treating cancer which comprises (a) a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salt and/or solvate thereof, and (b) an additional therapeutic agent, wherein a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea and the additional therapeutic agent are administered simultaneously, separately or sequentially, wherein the amounts of the crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salt and/or solvate thereof, and the additional therapeutic agent are together effective in treating the cancer. In some embodiments, the crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salt and/or solvate thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In some embodiments, the crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salt and/or solvate thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g., in daily or intermittently dosages. In some embodiments, the crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or pharmaceutically acceptable salt and/or solvate thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage.

Non-limiting examples of additional therapeutic agents include: other PI3K $\alpha$ -targeted therapeutic agents (i.e., other PI3K $\alpha$  inhibitors), EGFR inhibitors, VEGFR inhibitors/VEGF inhibitors, HER2 inhibitors, MEK pathway targeted therapeutic agents (including RAS pathway targeted therapeutic agents, which includes mTOR modulators/inhibitors, as described herein), SHP2 inhibitors, ULK inhibitors, cytotoxic chemotherapeutic, CDK2 inhibitors, Cyclin E inhibitors, CDK4 inhibitors, CDK6 inhibitors, CDK4/6 inhibitors, NTRK/ROS inhibitors, ALK inhibitors, RET inhibitors, MET inhibitors, PARP inhibitors, PIM (e.g., PIM1 and PIM3) inhibitors, other kinase inhibitors (e.g., receptor tyrosine kinase-targeted therapeutic agents (e.g.,

Trk inhibitors or multi-kinase inhibitors)), KAT6A inhibitors, farnesyl transferase inhibitors, aromatase inhibitors, selective estrogen receptor modulators or degraders (SERMs / SERDs, including ER $\alpha$  inhibitors or ER $\alpha$  degraders), vinca alkaloids, signal transduction pathway inhibitors, anti-metabolites, anti-androgens (e.g., androgen receptor (AR) antagonists, AR  
 5 degraders, AR modulators), alkylating agents, checkpoint inhibitors, modulators of the apoptosis pathway (e.g., obataclax), cytotoxic chemotherapeutics (also called antineoplastic chemotherapeutics), angiogenesis-targeted therapies (e.g., angiogenesis inhibitors), immune-targeted agents (including immunotherapy), radiotherapy, glucocorticoids, antidiarrheal agents (such as loperamide and diphenoxylate-atropine), antihistamines, and retinoic acid.

As used herein, a PIM inhibitor is any inhibitor of a Provirus Integration site for Moloney leukemia virus kinase (also sometimes referred to as Proviral Insertion site in Murine leukemia virus protein kinase), e.g., PIM1, PIM2, and PIM3, and any isoforms thereof (e.g., PIM-1L (molecular mass of 44 kDa) and PIM-1S (molecular mass of 33 kDa)). PIM kinases regulate cell proliferation, survival, metabolism, cellular trafficking and signaling and are overexpressed in a  
 15 number of human cancers. Non-limiting examples of PIM1 inhibitors include A47, abemaciclib (Verzenio; NCT03905889), AZD1208 (NCT01588548), AZD1897, ETH-155008, ETP-390101, ETP-45299, ETP-47551, INCB053914 (Uzansertib), JP11646, K00135, K00486, LGB321, LGH447 (PIM447), PIM447, SEL24/MEN1703 (SEL24-B489), SGI-1776, and TP-3654 (*See*, Belon and Nicot (2023) *Mol. Cancer* 22(1): 18; Mahata S., et al. (2022) *Med. Oncol.* 39(5): 74; Asasti V., et al. (2019) *Eur J Med Chem.* 172:95-108; Le X., et al. (2016) *Cancer Discov.* 6(10):  
 20 1134-47; Keeton EK, et al. (2014) *Blood* 123: 905-13; Garcia P., et al. (2013) *ASH* 122:1666; Grundler R, et al. (2009) *J Exp Med.* 206(9):1957-70; Pogacic V., et al., (2007) *Cancer Res.* 67(14):6916–6924).

Exemplary SHP2 inhibitors include JAB-3312, SHP099, SHP099 hydrochloride, SHP504, RMC-3943, AS1949490, SHP394, SHP389, and RMC-4630.  
 25

In some embodiments, the SHP2 inhibitor is RMC-4630.

Exemplary ULK inhibitors include ULK-101, SBP-7455, SBI-0206965, ULK1-IN-2, MRT68921, MRT68921 dihydrochloride, MRT67307, MRT67307 hydrochloride, XST-14, and GW406108X (CW108X).

Exemplary NTRK/ROS inhibitors include entrectinib (NMS-E628, RXDX-101, ROZLYTREK®), taletrectinib (DS-6051b, AB-106), or repotrectinib (TPX-0005),  
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Exemplary ALK inhibitors include crizotinib (XALKORI®, PF-02341066), ceritinib (ZYGADIA®, LDK-378), alectinib (ALECENSA®, CH5424802, RO5424802, AF802), brigatinib (ALUNBRIG®, AP-26113), lorlatinib (LORBRENA®, PF-06463922), entrectinib (NMS-E628, RXDX-101, ROZLYTREK®), ASP3026, TSR-011, PF-06463922, ensartinib (X-396), or CEP-37440.

Exemplary RET inhibitors include selpercatinib (RETEVMO®, LOXO-292), zeteletinib (BOS-172738, DS-5010), GSK3179106, amuvatinib hydrochloride (MP470 hydrochloride, HPK 56 hydrochloride), TPX-0046, or pralsetinib (GAVRETO®, BLU-667).

Exemplary MET inhibitors include capmatinib (TABRECTA®, INC280; INCB28060), tepotinib (TEPMETKO®), tivantinib (ARQ197), savolitinib (ORPATHYS®, Volitinib, HMPL-504, AZD-6094), foretinib (XL880, GSK1363089, GSK089, EXEL-2880), pamufetinib (TAS-115), c-Met-IN-2, PHA-665752, SU11274, SYN1143, or amuvatinib hydrochloride (MP470 hydrochloride, HPK 56 hydrochloride).

Exemplary TRK or multi-targeted kinase inhibitors include altiratinib (DCC-2701), CH7057288, larotrectinib (VITRAKVI®), entrectinib, ANA-12, repotrectinib (TPX-0005), sitravatinib (MGCD516, MG-516), lestaurtinib (CEP-701, KT-5555), tyrphostin AG 879 (AG 879), and selitrectinib (LOXO-195).

Exemplary tyrosine kinase inhibitors include axitinib (INLYTA®), dasatinib (SPRYCEL®), erlotinib (TARCEVA®), imatinib (GLIVEC), nilotinib (TASIGNA®), pazopanib (VOTRIENT®), sunitinib (SUTENT®), and vemurafenib.

Exemplary vinca alkaloids include vinorelbine, vinblastine, vincristine, vindesine, and vinflunine.

Exemplary antimetabolites include methotrexate, 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP), capecitabine (XELODA®), floxuridine, cytarabine (ARA-C®), fludarabine, gemcitabine (GEMZAR®), hydroxycarbamide, pemetrexed (ALIMTA®), phototrexate, decitabine, vidaza, DFP-11207, and RX-3117, TAS-114.

Exemplary alkylating agents include cyclophosphamide, lomustine, carmustine, streptozocin, bendamustine, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, chlorambucil, melphalan, busulfan, dacarbazine, temozolomide, altretamine, thiotepa, carboplatin, cisplatin, lurbinectedin, trabectedin, carmustine, oxaliplatin, and oxaliplatin.

Exemplary checkpoint inhibitors include nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, avelumab, ipilimumab, LAG525 (IMP701), REGN3767 (R3767), BI 754,091, tebotelimab (MGD013), eftilagimod alpha (IMP321), FS118, MBG453, Sym023, TSR-022, MGC018, FPA150, EOS100850, AB928, CPI-006, monalizumab, COM701, CM24, NEO-201, defactinib, PF-04136309, MSC-1, Hu5F9-G4 (5F9), ALX148, TTI-662, RRx-001, lacnotuzumab (MCS110), LY3022855, SNDX-6352, emactuzumab (RG7155), pexidartinib (PLX3397), CAN04, canakinumab (ACZ885), BMS-986253, pepinemab (VX15/2503), trebananib, FP-1305, enapotamab vedotin (EnaV), and bavituximab.

Exemplary modulators of the apoptosis pathway include obataclax, oblimersen, ABT-737, navitoclax (ABT-263), venetoclax (ABT-199), Z-VAD-FMK, emricasan, Q-VD-Oph, Z-VAD(OH)-FMK, belnacasan (caspase-1), Z-DEVD-FMK (caspase-3), Q-VD-OphZ-IETD-FMK (caspase-8), PAC-1 (procaspase-3), nutlin-3, nutlin-3a, idasanutlin, HDM201, APR-246, CBL0137, pifithrin- $\alpha$ , pifithrin- $\mu$ , Z-VAD-FMK, Emricasan, Q-VD-Oph, Z-VAD(OH)-FMK, pomalidomide, lenalidomide, YM155, Venetoclax (Bcl-2), S63845 (MCL-1), and A-1331852 (BCL-XL).

Exemplary cytotoxic chemotherapeutics include 5-fluorouracil, gemcitabine, methotrexate, NB1011, cyclophosphamide, dacarbazine, melphalan, tracectedin, temozolomide, doxorubicin, daunorubicin, mitoxantrone, vinblastine, paclitaxel, docetaxel, irinotecan, etoposide, and platinum agents such as carboplatin, cisplatin, and oxaliplatin.

Exemplary topoisomerase inhibitors include etoposide, irinotecan, camptothecin (CPT), topotecan (TPT), irinotecan, belotecan, indenoisoquinoline, phenanthridines, and indolocarbazoles. Additional examples of topoisomerase inhibitors include aminocamptothecin, CT-2106, crisnatol mesylate, DE-310, elinafide, lucanthone, MLN576, and mitindomide.

Exemplary angiogenesis-targeted therapies include bevacizumab, itraconazole, carboxyamidotriazole, TNP-470, CM101, IFN- $\alpha$ , IL-12, platelet factor-4, suramin, SU5416, thrombospondin, angiostatin, endostatin, 2-methoxyestradiol, tecogalan, tetrathiomolybdate, thalidomide, thrombospondin, prolactin, linomide, ramucirumab, tasquinimod, ranibizumab, sorafenib, sunitinib, pazopanib, everolimus, lenalidomide (e.g., REVLIMID®), and pomalidomide (e.g., POMALYST® or Imnovid®), marimistat, 2-methoxyestradiol (PANZEM), SU5415, SU6668, pemaxanib, sunitinib, vandetanib, vitaxin, YM598, ZD6126, and aflibercept.

In some embodiments, the angiogenesis targeted therapy is lenalidomide.

In some embodiments, the angiogenesis targeted therapy is pomalidomide.

In some embodiments, the EGFR inhibitor is osimertinib (AZD9291, merelectinib, TAGRISSO®), erlotinib (TARCEVA®), gefitinib (IRESSA®), cetuximab (ERBITUX®), necitumumab (PORTRAZZA®, IMC-11F8), neratinib (HKI-272, NERLYNX®), panitumumab (ABX-EGF, VECTIBIX®), vandetanib (CAPRELSA®), rociletinib (CO-1686), olmutinib (OLITA®, HM61713, BI-1482694), naquotinib (ASP8273), nazartinib (EGF816, NVS-816), maverlertinib (PF-06747775), icotinib (BPI-2009H), afatinib (BIBW 2992, GILOTRIF®), dacomitinib (PF-00299804, PF-804, PF-299, PF-299804), avitinib (AC0010), AC0010MA, EAI045, matuzumab (EMD-7200), nimotuzumab (h-R3, BIOMAb EGFR®), zalutumab, MDX447, depatuxizumab (humanized mAb 806, ABT-806), depatuxizumab mafodotin (ABT-414), ABT-806, mAb 806, canertinib (CI-1033), shikonin, shikonin derivatives (e.g., deoxyshikonin, isobutyrylshikonin, acetylshikonin,  $\beta,\beta$ -dimethylacrylshikonin and acetylalkannin), poziotinib (NOV120101, HM781-36B), AV-412, ibrutinib, WZ4002, brigatinib (AP26113, ALUNBRIG®), pelitinib (EKB-569), tarloxotinib (TH-4000, PR610), BPI-15086, Hemay022, ZN-e4, tesevatinib (KD019, XL647), lazertinib (YH25448), epitinib (HMPL-813), olafertinib (CK-101, RX518), MM-151, zorifertinib (AZD3759), vandetanib (ZD6474), PF-06459988, varlentinib (ASLAN001, ARRY-334543), mobocertinib (AP32788, TAK-788), pimirutamab (HLX07), befotertinib (D-0316), AEE788 (NVP-AEE788), aumolertinib (formerly almonertinib, HS-10296), avitinib, lapatinib (GW572016), pyrotinib (SHR1258), SCT200, CPGJ602, Sym004 (combination of futuximab and modotuximab), EMD 55900 (MAb-425), modotuximab (TAB-H49), futuximab (992 DS), zalutumumab, RO5083945, laprituximab emtansine (IMGN289), amivantamab (RYBREVANT™, JNJ-61186372), LY3164530, Pan-HER (Sym013), AMG 595, tuxobertinib (BDTX-189), avatinib, disruptin, CL-387785 (EKI-785, WAY-EKI 785), EGFRBi-Armed Autologous T Cells, and EGFR CAR-T Therapy. In some embodiments, the EGFR-targeted therapeutic agent is selected from gefitinib, erlotinib, afatinib, lapatinib, neratinib, osimertinib (AZD-9291, e.g., TAGRISSO®), CL-387785 (EKI-785, WAY-EKI 785), rociletinib (CO-1686), WZ4002, OMP-305B83, trastuzumab (e.g., TRAZIMERA™, HERCEPTIN®), RG-7597, and amivantanab.

In some embodiments, the EGFR inhibitor is lazertinib. In some embodiments, the EGFR inhibitor is amivantanab. In some embodiments, the EGFR inhibitor is trastuzumab.

Exemplary HER2 inhibitors include trastuzumab (e.g., TRAZIMERA™, HERCEPTIN®), pertuzumab (e.g., PERJETA®), trastuzumab emtansine (T-DM1 or ado-trastuzumab emtansine, e.g., KADCYLA®), fam-trastuzumab deruxtecan (ENHERTU®), lapatinib, KU004, neratinib (e.g., NERLYNX®), sacituzumab govitecan-hziy (TRODELVY®) dacomitinib (e.g., VIZIMPRO®), afatinib (GILOTRIF®), tucatinib (irbinitinib, ONT-380, ARRY-380, e.g., TUKYSA™), erlotinib (e.g., TARCEVA®), pyrotinib, poziotinib, CP-724714, CUDC-101, sapitinib (AZD8931), tanespimycin (17-AAG), IPI-504, dacomitinib (PF299804, PF299), pelitinib, margetuximab, AEE-788 (NVP-AEE788), enfortumab vedotin (PADCEV®), and datopotamab deruxtecan.

In some embodiments, the HER2 inhibitor is fam-trastuzumab deruxtecan. In some embodiments, the HER2 inhibitor is sacituzumab govitecan-hziy. In some embodiments, the HER2 inhibitor is datopotamab deruxtecan.

Exemplary VEGFR inhibitors/VEGF inhibitors include pazopanib, sunitinib, lenvatinib, cabozantinib, sorafenib, regorafenib, ponatinib, lenvatinib axitinib, ziv-aflibercept, vandetanib, tivozanib, vatalanib, AZD-2932, aflibercept, vanucizumab, BI836880, double antiangiogenic protein (DAAP), and ramucirumab.

A “MEK pathway targeted therapeutic agent” as used herein includes any compound exhibiting inactivation activity of any protein in a MEK pathway including any protein in the RAS pathway and the RAF pathway (e.g., kinase inhibition, allosteric inhibition, inhibition of dimerization, and induction of degradation) A “RAS pathway targeted therapeutic agent” as used herein includes any compound exhibiting inactivation activity of any protein in a RAS pathway (e.g., kinase inhibition, allosteric inhibition, inhibition of dimerization, and induction of degradation). Non-limiting examples of a protein in a RAS pathway include any one of the proteins in the RAS-RAF-MAPK pathway or PI3K/AKT pathway such as RAS (e.g., KRAS, HRAS, and NRAS), RAF (ARAF, BRAF, CRAF), MEK, ERK, PI3K, AKT, and mTOR. In some embodiments, a RAS pathway modulator can be selective for a protein in a RAS pathway, e.g., the RAS pathway modulator can be selective for RAS (also referred to as a RAS modulator). In some embodiments, a RAS modulator is a covalent inhibitor. In some embodiments, a RAS pathway targeted therapeutic agent is a “KRAS pathway modulator.” A KRAS pathway modulator includes any compound exhibiting inactivation activity of any protein in a KRAS pathway (e.g., kinase inhibition, allosteric inhibition, inhibition of dimerization, and induction of degradation).

Non-limiting examples of a protein in a KRAS pathway include any one of the proteins in the KRAS-RAF-MAPK pathway or PI3K/AKT pathway such as KRAS, RAF, BRAF, MEK, ERK, PI3K (i.e., other PI3K inhibitors, as described herein), AKT, and mTOR. In some embodiments, a KRAS pathway modulator can be selective for a protein in a RAS pathway, e.g., the KRAS pathway modulator can be selective for KRAS (also referred to as a KRAS modulator). In some  
5       embodiments, a KRAS modulator is a covalent inhibitor.

Non-limiting examples of RAS-targeted therapeutic agents include sotorasib (AMG 510, Lumakras®), adagrasib (MRTX849), tipifarnib (R115777, zarnestra), cismethynil, UCM-1336, deltarasin, NHTD, RM007, RM008, gefitinib, apatinib, oncrasin-1, vismodegib (GDC-0449), N-  
10       (1-Acryloylazetid-3-yl)-2-(5-bromo-3-(5-methoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-1H-indol-1-yl) acetamide, 2-((4-((1-(2-(2,4-Dichlorophenoxy) acetyl) piperidin-4-yl) amino)-4-oxobutyl) disulfaneyl)-N,N-dimethylethan-1-aminium, ARS-1620, ARS-853, bemcentinib (BGB324), ABT-737, selumetinib (AZD6244), dactolisib (NVP-BEZ235), PPIN-1, PPIN-2, pan-RAS Inhibitor 3144 (RAS-IN-3144), deltarasin, SML-8-73-1, SML-10-70-1, 1-(2-hydroxyethyl)-  
15       4-(2-methyl-3,5-diphenylpyrazolo[1,5-a] pyrimidin-7-yl) piperazin-1-ium, (2R,4aR)-3-acryloyl-11-chloro-9-fluoro-10-(6-fluoro-2-hydroxycyclohexa-2,4-dien-1-yl)-2,6-dimethyl-2,3,4,4a-tetrahydro-1H-pyrazino [1',2':4,5] pyrazino[2,3-c] quinolin-5(6H)-one, NHTD, PD98059, wortmannin, talniflumate, gefitinib, CPD-0857, KY1022, KYA1797K (ab229170), 0375-0604 (DUN09716), 7773, NSC-658497, JNJ-74699157, PKF115-584 (calphostin C), Kobe0065,  
20       Kobe2602, salirasib, 3,3'-(ethylazanediyl)bis(N-phenylpropanamide), ML264, GDC-6036, LY3499446, and D-1553.

Non-limiting examples of KRAS-targeted therapeutic agents (e.g., KRAS inhibitors) include BI 1701963, sotorasib (AMG 510), ARS-3248 (JNJ-74699157), ARS1620, AZD4785 (ION651987), SML-8-73-1, SML-10-70-1, VSA9, AA12, adagrasib (MRTX-849), LY3499446,  
25       ARS853, and siG12D LODER.

Non-limiting examples of HRAS-targeted therapeutic agent (e.g., HRAS inhibitors) include tipifarnib (ZARNESTRA®). Further non-limiting examples of RAS-targeted therapeutic agents include BRAF inhibitors, MEK inhibitors, ERK inhibitors, PI3K inhibitors, AKT inhibitors, and mTOR inhibitors. In some embodiments, the

30       In some embodiments, the MEK inhibitor is trametinib (MEKINIST®, GSK1120212), cobimetinib (COTELLIC®), binimetinib (MEKTOVI®, MEK162), selumetinib (AZD6244),

mirdametinib (PD0325901), pimasertib (MSC1936369B), SHR7390, TAK-733, RO5126766 (CH5126766), CS3006, WX-554, PD98059, CI1040 (PD184352), hypothemycin, or a combination thereof.

In some embodiments, the ERK inhibitor is amerliorex (FRI-20, ON-01060), VTX-11e, 25-OH-D3-3-BE (B3CD, bromoacetoxycalcidiol), FR-180204, AEZ-131 (AEZS-131), AEZS-136, AZ-13767370, BL-EI-001, temuterkib (LY-3214996), rineterkib (LTT-462), KO-947, MK-8353 (SCH900353), SCH772984, ulixertinib (BVD-523), CC-90003, ravoxertinib (GDC-0994, RG-7482), ASN007, 5Z-7-oxozeaenol (FR148083, L783279, LL-Z 1640-2), 5-iodotubercidin (NSC 113939), ONC201 (TIC10), or a combination thereof.

In some embodiments, the anti-androgen is leuprolide (LUPRON®), ELIGARD®, goserelin (ZOLDEX®), triptorelin (TRELSTAR®), leuprolide mesylate (CAMCEVI®), flutamide (EULEXIN®), bicalutamide (CASODEX®), nilutamide (NILANDRON®), degarelix (FIRMAGON®), relugolix (ORGOVYX®), enzalutamide (MDV3100, XTANDI®), abiraterone (ZYTIGA®), flutamide (EULEXIN®), AR inhibitor EPI-506, apalutamide (ERLEADA®), and darolutamide (NUBEQA®).

In some embodiments, the other PI3K inhibitor is another PI3K $\alpha$  inhibitor. In some embodiments, the other PI3K inhibitor is a pan-PI3K inhibitor. In some embodiments, the other PI3K inhibitor is selected from buparlisib (BKM120), alpelisib (BYL719, PIQRAY®), RLY-2608, idelalisib, duvelisib, umbralisib, WX-037, copanlisib (ALIQOPA®, BAY80-6946), dactolisib (NVP-BEZ235, BEZ-235), taselisib (GDC-0032, RG7604), sonolisib (PX-866), fimepinostat (CUDC-907), bimiralisib (PQR309), ZSTK474, SF1126, AZD8835, inavolisib (GDC-0077), ASN003, pictilisib (GDC-0941), pilaralisib (XL147, SAR245408), gedatolisib (PF-05212384, PKI-587), serabelisib (TAK-117, MLN1117, INK 1117), BGT-226 (NVP-BGT226), PF-04691502, apitolisib (GDC-0980), omipalisib (GSK2126458, GSK458), voxtalisib (XL756, SAR245409), AMG 511, CH5132799, GSK1059615, paxalisib (GDC-0084, RG7666), VS-5584 (SB2343), PKI-402, wortmannin, LY294002, PI-103, rigosertib (ON-01910 sodium salt), voxtalisib (XL-765), LY2023414, SAR260301, KIN-193 (AZD-6428), acalisib (GS-9820), AMG319, GSK2636771, or a combination thereof.

In some embodiments, the AKT inhibitor is selected from miltefosine (IMPADIVO®), wortmannin, NL-71-101, H-89, GSK690693, CCT128930, capivasertib (AZD5363), ipatasertib (GDC-0068, RG7440), A-674563, A-443654, AT7867, AT13148, uprosertib (GSK2141795),

afuresertib (GSK2110183), DC120, 2-[4-(2-aminoprop-2-yl)phenyl]-3-phenylquinoxaline, MK-2206, edelfosine, miltefosine, perifosine (KRX-0401), erucylphosphocholine, erufosine, SR13668, OSU-A9, PH-316, PHT-427 (CS-0223), PIT-1, DM-PIT-1, triciribine (Triciribine Phosphate Monohydrate), API-1, N-(4-(5-(3-acetamidophenyl)-2-(2-aminopyridin-3-yl)-3H-imidazo[4,5-b]pyridin-3-yl)benzyl)-3-fluorobenzamide, miransertib (ARQ092), BAY 1125976, 3-oxo-tirucallic acid, lactoquinomycin, boc-Phe-vinyl ketone, Perifosine (D-21266), TCN, TCN-P, ONC201 (TIC10), and TAS117.

In some embodiments, the AKT inhibitor is capivasertib.

In some embodiments, the mTOR inhibitor is an analog of rapamycin. Examples of analogs of rapamycin include sapanisertib (MLN0128), vistusertib (AZD-2014), onatasertib (CC-223), CC-115, everolimus (RAD001), temsirolimus (CCI-779), ridaforolimus (AP-23573), sirolimus (rapamycin), ridaforolimus (MK-8669), everolimus (RAD001, e.g., AFINITOR® or ZORTRESS®), umirolimus, zotarolimus, and RMC-5552. In some embodiments, the mTOR inhibitor is an ATP-competitive mTOR kinase inhibitor, which compete with ATP in the catalytic site of mTOR. Examples of ATP-competitive mTOR kinase inhibitors can include torin-1, torin-2, and vistusertib. Types of ATP-competitive mTOR kinase inhibitors can include mTOR/PI3K dual inhibitors and mTORC1/mTORC2 dual inhibitors (also called TORCdIs). Examples of mTOR/PI3K dual inhibitors include dactolisib, voxalisib, BGT226, SF1126, PKI-587, NVPBE235. Example of mTORC1/mTORC2 dual inhibitors include sapanisertib (codenamed INK128), AZD8055, and AZD2014.

Non-limiting examples of farnesyl transferase inhibitors include lonafarnib, tipifarnib, BMS-214662, L778123, L744832, and FTI-277.

In some embodiments, a chemotherapeutic agent includes an anthracycline, alkylating agents, a taxane, a platinum-based agent, mitomycin, gemcitabine, pemetrexed, eribulin (HALAVEN<sup>TM</sup>), or combinations thereof.

Non-limiting examples of a taxane include paclitaxel, docetaxel, abraxane, and taxotere.

In some embodiments, the anthracycline is selected from daunorubicin, doxorubicin, epirubicin, idarubicin.

In some embodiments, the platinum-based agent is selected from carboplatin, cisplatin, oxaliplatin, nedplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, satraplatin, and lobaplatin. Any of the platinum-based agents can be conjugated to a nanocarrier, such as a gold nanocluster,

a gold nanoparticle, or a superparamagnetic iron oxide nanoparticles. See, for example, Zhang et al. 2022. *Theranostics*. 12(5):2115-2132.

Non-limiting examples of PARP inhibitors include olaparib (LYNPARZA®), talazoparib, rucaparib, niraparib, veliparib, BGB-290 (pamiparib), CEP-9883, CEP 9722, E7016 (GPI 21016), iniparib, senaparib (IMP4297), venadaparib-idience (NOV1401, IDX-1197), stenoparib (2X-121), ABT-767, atamparib (RBN-2397), talazoparib (BMN 673), olaparib (KU-0059436, AZD2281, e.g. LYNPARZA™), iniparib (BSI-201, SAR240550), rucaparib (A G-014699, PF-01367338), INO-1001, and amelparib (JPI-289).

Non-limiting examples of aromatase inhibitors include aminoglutethimide, testolactone, anastrozole, letrozole, exemestane, vorozole, formestane, and fadrozole.

Non-limiting examples of selective estrogen receptor modulators or degraders (SERMs / SERDs) include clomifene, cyclofenil, anordrin, broparestrol, nafoxidine, ormeloxifene, raloxifene, toremifene, lasofoxifene, bazedoxifene, ospemifene, afimoxifene, enclomiphene, serophene, arzoxifene, tamoxifen, etacstil (GW-5638, DPC974), fulvestrant (FASLODEX®), brilanestrant, elacestrant (ORSERDU™), giredestrant, amcenestrant (SAR439859), camizestrant (AZD9833), rintodestrant, imlunestrant, LSZ102, LY3484356, ZN-c5, taragarestrant (D-0502), AZD9496, clotrimazole, fenticonazole, SHR9549, and palazestrant (OP-1250).

In some embodiments, the SERM/SERD is palazestrant. In some embodiments, the SERM/SERD is elacestrant. In some embodiments, the SERM/SERD is camizestrant.

Non-limiting examples of glucocorticoids include dexamethasone, beclomethasone, betamethasone, budesonide, cortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone.

In some embodiments, the glucocorticoid is dexamethasone.

In some embodiments, the additional therapeutic agent is retinoic acid.

Non-limiting examples of epigenetic agents include EZH2 inhibitors (e.g., tazemetostat, such as TAZVERIK®, 3-deazaneplanocin A (DZNep or C-c3Ado), EPZ005687, EI1, GSK126, and UNC1999) and HDAC inhibitors (e.g., vorinostat (SAHA) and panobinostat (LBH589)). Non-limiting examples of HDAC inhibitors include hydroxamic acids (or hydroxamates), such as trichostatin A, vorinostat (SAHA), belinostat (PXD101), LAQ824, and panobinostat (LBH589); cyclic tetrapeptides, such as trapoxin B, and depsipeptides; benzamides, such as entinostat (MS-



275), tacedinaline (CI994), and mocetinostat (MGCD0103); electrophilic ketones; and aliphatic acid compounds such as phenylbutyrate and valproic acid.

In some embodiments, the epigenetic agent is an EZH2 inhibitor. In some embodiments, the epigenetic agent is tazemetostat. In some embodiments, the EZH2 inhibitor is tazemetostat.

5 In some embodiments, the epigenetic agent is a HDAC inhibitor. In some embodiments, the epigenetic agent is vorinostat. In some embodiments, the epigenetic agent is panobinostat. In some embodiments, the HDAC inhibitor is vorinostat. In some embodiments, the HDAC inhibitor is panobinostat.

Non-limiting examples of KAT6A inhibitors include WM-8014, PF-07248144, CTx-  
10 648 (PF-9363), and CTX-0124143. In some embodiments, the KAT6A inhibitor is WM-8014. In some embodiments, the KAT6A inhibitor is PF-07248144. In some embodiments, the KAT6A inhibitor is CTx-648. In some embodiments, the KAT6A inhibitor is CTX-0124143.

Non-limiting examples of immunotherapy include immune checkpoint therapies,  
15 atezolizumab (TECENTRIQ®), albumin-bound paclitaxel. Non-limiting examples of immune checkpoint therapies include inhibitors that target CTLA-4, PD-1, PD-L1, BTLA, LAG-3, A2AR, TIM-3, B7-H3, VISTA, IDO, and combinations thereof. In some embodiments the CTLA-4 inhibitor is ipilimumab (YERVOY®). In some embodiments, the PD-1 inhibitor is selected from nivolumab (OPDIVO®), pembrolizumab (KEYTRUDA®), cemiplimab (LIBTAYO®),  
20 atezolizumab (TECENTRIQ®), durvalumab (IMFINZI®), avelumab (BAVENCIO®), dostarlimab (JEMPERLI®), retifanlimab (ZYNLYS®), vopratelimab (JTX-4014), spartalizumab (PDR001), camrelizumab (SHR1210), sintilimab (IBI308), tislelizumab (BGB-A317), toripalimab (JS 001), INCMGA00012 (MGA012), AMP-224, AMP-514 (MEDI0680), or Acrixolimab (YBL-006). In some embodiments, the PD-1 inhibitor is selected from pembrolizumab (KEYTRUDA®),  
25 nivolumab (OPDIVO®), cemiplimab (LIBTAYO®), or combinations thereof. In some embodiments, the PD-L1 inhibitor is selected from atezolizumab (TECENTRIQ®), avelumab (BAVENCIO®), durvalumab (IMFINZI®), or combinations thereof. In some embodiments, the LAG-3 inhibitor is leramilimab (IMP701, LAG525). In some embodiments, the A2AR inhibitor is ciforadenant (CPI-444). In some embodiments, the TIM-3 inhibitor is sabatolimab (MBG453).  
30 In some embodiments, the B7-H3 inhibitor is enoblituzumab. In some embodiments, the VISTA

inhibitor is onvatilimab (JNJ-61610588). In some embodiments, the IDO inhibitor is indoximod. See, for example, Table 1 of Marin-Acevedo, et al., *J Hematol Oncol.* 11: 39 (2018), which is incorporated in its entirety herein.

In some embodiments, the CDK2 inhibitor is selected from INX-315, BLU-222,  
5 INCB123667, AZD8421, and Tagtociclib (PF-07104091).

In some embodiments, the CDK4 inhibitor is PF-07220060.

In some embodiments, the cytotoxic chemotherapeutic is selected from abraxane, actinomycin, alitretinoin, all-trans retinoic acid, altretamine, azacitidine, azathioprine, belotecan, bendamustine, bexarotene, bleomycin, bortezomib, busulfan, cabazitaxel, camptothecin,  
10 carboplatin, carboquone, carmustine, capecitabine, cisplatin, chlorambucil, chlormethine, chlorozotocin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, decitabine, docetaxel, doxifluridine, doxorubicin, epirubicin, epothilone, erlotinib, etoposide, exatecan, fludarabine, fluorouracil, fotemustine, gefitinib, gemcitabine, gimatecan, idarubicin, ifosfamide, imatinib, irinotecan, ixabepilone, larotaxel, lomustine, melphalan, mercaptopurine,  
15 methotrexate, mitobronitol, mitomycin C, mitoxantrone, nelarabine, nimustine, oxaliplatin, paclitaxel, pemetrexed, tafluposide, taxotere, temozolomide, tesetaxel, teniposide, thiotepa, topotecan, tretinoin, alrubicin, vemurafenib, vinblastine, vincristine, vindesine, vinorelbine, vismodegib, and vorinostat.

In some embodiments, the CDK4/6 inhibitor is selected from palbociclib (IBRANCE®,  
20 TQB3616, PD-0332991), ribociclib (KISQALI®), abemaciclib (VERZENIO®), voruciclib (P1446A-05), trilaciclib, dalpiciclib (SHR6390), roniciclib (BAY1000394), dinaciclib, flavopiridol (alvociclib, L868275, HMR-1275), roscovitine (R-roscovitine, CYC202, seliciclib), riviciclib (P276-00, P276), AT7519, TG02 (SB1317), RGB-286638, dinaciclib (SCH 727965), PHA-793887, ZK-304709, xytocydine, SNS032 (BMS-387032), R547 (R<sub>0</sub> 4584820),  
25 RGB286147, prvalanol A (NG60), meriolin 3, JNJ7706621, indirubin, AZD-5438, 10Z-hymenialdisine, AGO24322, PF-06873600, and KIN-8741.

In some embodiments, the CDK4/6 inhibitor is KIN-8741. In some embodiments, the CDK4/6 inhibitor is palbociclib. In some embodiments, the CDK4/6 inhibitor is ribociclib. In some  
30 embodiments, the CDK4/6 inhibitor is trilaciclib. In some embodiments, the CDK4/6 inhibitor is dalpiciclib. In some embodiments, the CDK4/6 inhibitor is voruciclib. In some embodiments, the CDK4/6 inhibitor is roniciclib. In some embodiments, the CDK4/6 inhibitor is dinaciclib.

In some embodiments, the additional therapy or therapeutic agent is selected from fulvestrant, capecitabine, trastuzumab, ado-trastuzumab emtansine, pertuzumab, paclitaxel, nab-paclitaxel, enzalutamide, olaparib, pegylated liposomal doxorubicin (PLD), trametinib, palbociclib (IBRANCE®), buparlisib, sotrastaurin (AEB071), everolimus, exemestane, cisplatin, letrozole, ganitumab (AMG 479), LSZ102, ribociclib (LEE011), cetuximab, luminespib (NVP-AUY922, AUY922), infigratinib (BGJ398), binimetinib (MEK162, ARRY-162, ARRY-438162), LJM716, PIM447 (LGH447, LGB321), imatinib, gemcitabine, encorafenib (LGX818), and amcenestrant.

In some embodiments, the additional therapeutic agent is everolimus. In some embodiments, additional therapeutic agents may also be administered to treat potential side-effects for particular anticancer therapies and/or as palliative therapy, for example, opioids and corticosteroids. In some embodiments, the additional therapy or therapeutic agent described herein is selected from the group consisting of a glucagon-like peptide-1 (GLP-1) receptor agonist, a sodium-glucose transport protein 2 (SGLT-2) inhibitor, a dipeptidyl peptidase 4 (DPP-4) inhibitor, metformin, and combinations thereof.

Non-limiting examples of GLP-1 receptor agonists include liraglutide (NN2211, e.g., VICTOZA®), dulaglutide (LY2189265, e.g., TRULICITY®), exenatide (e.g., BYETTA®, BYDUREON®, Exendin-4), taspoglutide, lixisenatide (e.g., LYXUMIA®), albiglutide (e.g., TANZEUM®), semaglutide (e.g., OZEMPIC®, RYBELSUS®), ZP2929, NNC0113-0987 (QBR110395), BPI-3016, and TT401.

Non-limiting examples of SGLT-2 inhibitors include bexagliflozin, canagliflozin (e.g., INVOKANA®), dapagliflozin (e.g., FARXIGA®), empagliflozin (e.g., JARDIANCE®), ertugliflozin (e.g., STEGLATRO™), ipragliflozin (e.g., SUGLAT®), luseogliflozin (e.g., LUSEFI®), remogliflozin, serfliflozin, licofliglozin, sotagliflozin (e.g., ZYNQUISTA™), and tofogliflozin.

Non-limiting examples of DPP-4 inhibitors include, sitagliptin (e.g., JANUVIA®), vildagliptin, saxagliptin (e.g., ONGLYZA®), linagliptin (e.g., TRADJENDA®), gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin (e.g., NESINA®), omarigliptin, evogliptin, and dutogliptin.

In some embodiments, the additional therapeutic agent is metformin. In some embodiments, the methods described herein further comprise administering a therapeutically effective amount of metformin to the subject.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one additional therapeutic agent, for example, an aromatase inhibitor, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a SERM/SERD, radiation therapy, an anti-HER2 antibody or antibody-drug conjugate (ADC) thereof, an immunotherapy, a checkpoint inhibitor (e.g., an anti-PD-1 or PD-L1 antibody, an anti-CLTA4 antibody), VEGFR inhibitors/VEGF inhibitors, KAT6A inhibitors (also called MOZ inhibitors or MYST3 inhibitors), PI3K $\alpha$  inhibitors, MEK pathway targeted therapeutic agents (including RAS pathway targeted therapeutic agents, which includes mTOR inhibitors, as described herein), SHP2 inhibitors, ULK inhibitors, NTRK/ROS inhibitors, ALK inhibitors, RET inhibitors, MET inhibitors, PARP inhibitors, PIM (e.g., PIM1 and PIM3) inhibitors, other kinase inhibitors (e.g., Trk inhibitors or multi-kinase inhibitors), farnesyl transferase inhibitors, vinca alkaloids, anti-metabolites, anti-androgens, alkylating agents, checkpoint inhibitors, modulators of the apoptosis pathway; cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents including immunotherapy, or an anti-EGFR antibody.

In some embodiments, the additional therapeutic agent is an antibody or ADC as described herein. In some embodiments, the antibody is daratumumab (e.g., DARZALEX®).

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one additional therapeutic agent, for example, a HER2 inhibitor, a SERM / SERD, a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a MEK inhibitor, a checkpoint inhibitor (e.g., an anti-PD-1 or PD-L1 antibody, an anti-CLTA4 antibody), a multi-kinase inhibitor, and a PI3K inhibitor.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and one additional therapeutic agent, for

example, trastuzumab, pertuzumab, trastuzumab emtansine, fam-trastuzumab deruxtecan, lapatinib, neratinib, dacomitinib, afatinib, tucatinib, erlotinib, pyrotinib, tanespimycin, dacomitinib, pelitinib, margetuximab, clomifene, cyclofenil, broparestrol, ormeloxifene, raloxifene, toremifene, lasofoxifene, bazedoxifene, ospemifene, enclomiphene, serophene, tamoxifen, fulvestrant, elacestrant, camizestrant, rintodestrant, clotrimazole, fenticonazole, nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, avelumab, ipilimumab, palbociclib, ribociclib, abemaciclib, trilaciclib, dalpiciclib, trametinib, cobimetinib, binimetinib, selumetinib, mirdametinib, pimasertib, alpelisib, RLY-2608, idelalisib, duvelisib, copanlisib, umbralisib, ribociclib, triaciclib, dalpiciclib, voruciclib, and roniciclib.

- 10           In some embodiments, the additional therapeutic agent is fulvestrant.  
              In some embodiments, the additional therapeutic agent is lapatinib.  
              In some embodiments, the additional therapeutic agent is abemaciclib.  
              In some embodiments, the additional therapeutic agent is trametinib.  
              In some embodiments, the additional therapeutic agent is binimetinib.
- 15           In some embodiments, the additional therapeutic agent is alpelisib.  
              In some embodiments, the additional therapeutic agent is RLY-2608.  
              In some embodiments, the additional therapeutic agent is palbociclib.  
              In some embodiments, the additional therapeutic agent is ribociclib.  
              In some embodiments, the additional therapeutic agent is trilaciclib.
- 20           In some embodiments, the additional therapeutic agent is dalpiciclib.  
              In some embodiments, the additional therapeutic agent is voruciclib.  
              In some embodiments, the additional therapeutic agent is roniciclib.  
              In some embodiments, the additional therapeutic agent is dinaciclib.  
              In some embodiments, the additional therapeutic agents are palbociclib and clomifene.
- 25           In some embodiments, the additional therapeutic agents are palbociclib and cyclofenil.  
              In some embodiments, the additional therapeutic agents are palbociclib and anordrin.  
              In some embodiments, the additional therapeutic agents are palbociclib and broparestrol.  
              In some embodiments, the additional therapeutic agents are palbociclib and nafoxidine.  
              In some embodiments, the additional therapeutic agents are palbociclib and ormeloxifene.
- 30           In some embodiments, the additional therapeutic agents are palbociclib and raloxifene.  
              In some embodiments, the additional therapeutic agents are palbociclib and toremifene.

In some embodiments, the additional therapeutic agents are palbociclib and lasofoxifene.  
In some embodiments, the additional therapeutic agents are palbociclib and bazedoxifene.  
In some embodiments, the additional therapeutic agents are palbociclib and ospemifene.  
In some embodiments, the additional therapeutic agents are palbociclib and afimoxifene.  
5 In some embodiments, the additional therapeutic agents are palbociclib and enclomiphene.  
In some embodiments, the additional therapeutic agents are palbociclib and serophene.  
In some embodiments, the additional therapeutic agents are palbociclib and arzoxifene.  
In some embodiments, the additional therapeutic agents are palbociclib and tamoxifen.  
In some embodiments, the additional therapeutic agents are palbociclib and etacstil.  
10 In some embodiments, the additional therapeutic agents are palbociclib and fulvestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and brilanestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and elacestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and giredestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and amcenestrant.  
15 In some embodiments, the additional therapeutic agents are palbociclib and camizestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and rintodestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and imlunestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and LSZ102.  
In some embodiments, the additional therapeutic agents are palbociclib and LY3484356.  
20 In some embodiments, the additional therapeutic agents are palbociclib and ZN-c5.  
In some embodiments, the additional therapeutic agents are palbociclib and taragarestrant.  
In some embodiments, the additional therapeutic agents are palbociclib and AZD9496.  
In some embodiments, the additional therapeutic agents are palbociclib and clotrimazole.  
In some embodiments, the additional therapeutic agents are palbociclib and fenticonazole.  
25 In some embodiments, the additional therapeutic agents are palbociclib and SHR9549.  
In some embodiments, the additional therapeutic agents are palbociclib and palazestrant.  
In some embodiments, the additional therapeutic agents are ribociclib and clomifene.  
In some embodiments, the additional therapeutic agents are ribociclib and cyclofenil.  
In some embodiments, the additional therapeutic agents are ribociclib and anordrin.  
30 In some embodiments, the additional therapeutic agents are ribociclib and broparestrol.  
In some embodiments, the additional therapeutic agents are ribociclib and nafoxidine.

- In some embodiments, the additional therapeutic agents are ribociclib and ormeloxifene.
- In some embodiments, the additional therapeutic agents are ribociclib and raloxifene.
- In some embodiments, the additional therapeutic agents are ribociclib and toremifene.
- In some embodiments, the additional therapeutic agents are ribociclib and lasofoxifene.
- 5 In some embodiments, the additional therapeutic agents are ribociclib and bazedoxifene.
- In some embodiments, the additional therapeutic agents are ribociclib and ospemifene.
- In some embodiments, the additional therapeutic agents are ribociclib and afimoxifene.
- In some embodiments, the additional therapeutic agents are ribociclib and enclomiphene.
- In some embodiments, the additional therapeutic agents are ribociclib and serophene.
- 10 In some embodiments, the additional therapeutic agents are ribociclib and arzoxifene.
- In some embodiments, the additional therapeutic agents are ribociclib and tamoxifen.
- In some embodiments, the additional therapeutic agents are ribociclib and etacstil.
- In some embodiments, the additional therapeutic agents are ribociclib and fulvestrant.
- In some embodiments, the additional therapeutic agents are ribociclib and brilanestrant.
- 15 In some embodiments, the additional therapeutic agents are ribociclib and elacestrant.
- In some embodiments, the additional therapeutic agents are ribociclib and giredestrant.
- In some embodiments, the additional therapeutic agents are ribociclib and amcenestrant.
- In some embodiments, the additional therapeutic agents are ribociclib and camizestrant.
- In some embodiments, the additional therapeutic agents are ribociclib and rintodestrant.
- 20 In some embodiments, the additional therapeutic agents are ribociclib and imlunestrant.
- In some embodiments, the additional therapeutic agents are ribociclib and LSZ102.
- In some embodiments, the additional therapeutic agents are ribociclib and LY3484356.
- In some embodiments, the additional therapeutic agents are ribociclib and ZN-c5.
- In some embodiments, the additional therapeutic agents are ribociclib and taragarestrant.
- 25 In some embodiments, the additional therapeutic agents are ribociclib and AZD9496.
- In some embodiments, the additional therapeutic agents are ribociclib and clotrimazole.
- In some embodiments, the additional therapeutic agents are ribociclib and fenticonazole.
- In some embodiments, the additional therapeutic agents are ribociclib and SHR9549.
- In some embodiments, the additional therapeutic agents are ribociclib and palazestrant.
- 30 In some embodiments, the additional therapeutic agents are abemaciclib and clomifene.
- In some embodiments, the additional therapeutic agents are abemaciclib and cyclofenil.

In some embodiments, the additional therapeutic agents are abemaciclib and anordrin.

In some embodiments, the additional therapeutic agents are abemaciclib and broparestrol.

In some embodiments, the additional therapeutic agents are abemaciclib and nafoxidine.

In some embodiments, the additional therapeutic agents are abemaciclib and ormeloxifene.

5 In some embodiments, the additional therapeutic agents are abemaciclib and raloxifene.

In some embodiments, the additional therapeutic agents are abemaciclib and toremifene.

In some embodiments, the additional therapeutic agents are abemaciclib and lasofoxifene.

In some embodiments, the additional therapeutic agents are abemaciclib and bazedoxifene.

In some embodiments, the additional therapeutic agents are abemaciclib and ospemifene.

10 In some embodiments, the additional therapeutic agents are abemaciclib and afimoxifene.

In some embodiments, the additional therapeutic agents are abemaciclib and enclomiphene.

In some embodiments, the additional therapeutic agents are abemaciclib and serophene.

In some embodiments, the additional therapeutic agents are abemaciclib and arzoxifene.

15 In some embodiments, the additional therapeutic agents are abemaciclib and tamoxifen.

In some embodiments, the additional therapeutic agents are abemaciclib and etacstil.

In some embodiments, the additional therapeutic agents are abemaciclib and fulvestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and brilanestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and elacestrant.

20 In some embodiments, the additional therapeutic agents are abemaciclib and giredestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and amcenestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and camizestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and rintodestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and imlunestrant.

25 In some embodiments, the additional therapeutic agents are abemaciclib and LSZ102.

In some embodiments, the additional therapeutic agents are abemaciclib and LY3484356.

In some embodiments, the additional therapeutic agents are abemaciclib and ZN-c5.

In some embodiments, the additional therapeutic agents are abemaciclib and taragarestrant.

In some embodiments, the additional therapeutic agents are abemaciclib and AZD9496.

30 In some embodiments, the additional therapeutic agents are abemaciclib and clotrimazole.

In some embodiments, the additional therapeutic agents are abemaciclib and fenticonazole.



In some embodiments, the additional therapeutic agents are abemaciclib and SHR9549.

In some embodiments, the additional therapeutic agents are abemaciclib and palazestrant.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and two additional independently selected therapeutic agents, for example, a HER2 inhibitor, a SERM / SERD, a cytotoxic chemotherapeutic, a CDK2 inhibitor, a Cyclin E inhibitor, a CDK4 inhibitor, a CDK6 inhibitor, a CDK4/6 inhibitor, a MEK inhibitor, a checkpoint inhibitor (e.g., an anti-PD-1 or PD-L1 antibody, an anti-CLTA4 antibody), a multi-kinase inhibitor, and a PI3K inhibitor.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and two additional independently selected therapeutic agents, for example, trastuzumab, pertuzumab, trastuzumab emtansine, fam-trastuzumab deruxtecan, lapatinib, neratinib, dacomitinib, afatinib, tucatinib, erlotinib, pyrotinib, tanespimycin, dacomitinib, pelitinib, margetuximab, clomifene, cyclofenil, broparestrol, ormeloxifene, raloxifene, toremifene, lasofoxifene, bazedoxifene, ospemifene, enclomiphene, serophene, tamoxifen, fulvestrant, elacestrant, camizestrant, rintodestrant, clotrimazole, fenticonazole, nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, avelumab, ipilimumab, palbociclib, ribociclib, abemaciclib, trilaciclib, dalpiciclib, trametinib, cobimetinib, binimetinib, selumetinib, mirdametinib, pimasertib, alpelisib, RLY-2608, idelalisib, duvelisib, copanlisib, umbralisib, ribociclib, triaciclib, dalpiciclib, voruciclib, and roniciclib.

In some embodiments, the additional therapeutic agents are fulvestrant and lapatinib.

In some embodiments, the additional therapeutic agents are fulvestrant and abemaciclib.

In some embodiments, the additional therapeutic agents are fulvestrant and trametinib.

In some embodiments, the additional therapeutic agents are fulvestrant and binimetinib.

In some embodiments, the additional therapeutic agents are fulvestrant and alpelisib.

In some embodiments, the additional therapeutic agents are fulvestrant and RLY-2608.

In some embodiments, the additional therapeutic agents are fulvestrant and palbociclib.

In some embodiments, the additional therapeutic agents are fulvestrant and dalpiciclib.

In some embodiments, the additional therapeutic agents are fulvestrant and voruciclib.

In some embodiments, the additional therapeutic agents are fulvestrant and roniciclib.

In some embodiments, the additional therapeutic agents are fulvestrant and dinaciclib.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and an ER $\alpha$  inhibitor or degrader.

5 In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and a cytotoxic chemotherapeutic.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a  
10 pharmaceutically acceptable salt thereof, and a CDK2 inhibitor.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and a Cyclin E inhibitor,

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a  
15 pharmaceutically acceptable salt thereof, and a CDK4 inhibitor.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and a CDK6 inhibitor.

20 In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and a CDK4/6 inhibitor.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a  
25 pharmaceutically acceptable salt thereof, and a HER2 inhibitor.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and alpelisib.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a  
30 pharmaceutically acceptable salt thereof, and fulvestrant.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and lapatinib.

5 In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and abemaciclib.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and a MEK inhibitor.

10 In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and trametinib.

In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and binimetinib.

15 In some embodiments, the method comprises administering a crystalline form of 1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt thereof, and palbociclib.

#### 20 *Dosing of Combinations*

In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a combination therapy (such as a double or triple combination) with one or more additional therapeutic agents, wherein the dose of the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is about 10 mg to about 200 mg per day, for example, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, or about 200 mg.

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In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a combination therapy (such as a double or triple combination) with one or more additional therapeutic agents, wherein the dose of the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is about 20 mg to about 160 mg per day, for example, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, or about 160 mg.

In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a combination therapy (such as a double or triple combination) with one or more additional therapeutic agents, wherein the dose of the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is about 20 mg to about 200 mg per day, for example, about 20 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, or about 200 mg.

In some embodiments, the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is administered to a subject as a combination therapy (such as a double or triple combination) with one or more additional therapeutic agents, wherein the dose of the crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, is about 60 mg to about 160 mg per day, for example, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 140 mg, or about 160 mg.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and fulvestrant. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and fulvestrant, wherein fulvestrant is administered at a dose in a range of about 250 mg to about 500 mg. In some embodiments, the method comprises administering a

crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and fulvestrant, wherein fulvestrant is administered at a dose of about 250 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and fulvestrant, wherein fulvestrant is administered at a dose of about 500 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and fulvestrant, wherein fulvestrant is administered as two 5 mL injections on days 1, 15, 29 and once monthly thereafter, where each 5 mL injection includes 250 mg of fulvestrant.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and lapatinib. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and lapatinib, wherein lapatinib is administered at a dose in a range of about 1250 mg to about 1500 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and lapatinib, wherein lapatinib is administered at a dose of about 1250 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and lapatinib, wherein lapatinib is administered at a dose of about 1500 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and lapatinib, wherein lapatinib is administered as 5 tablets once daily, where each tablet includes 250 mg of lapatinib. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a

pharmaceutically acceptable salt and/or solvate thereof, and lapatinib, wherein lapatinib is administered as 6 tablets once daily, where each tablet includes 250 mg of lapatinib.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein abemaciclib is administered at a dose in a range of about 150 mg to about 400 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein abemaciclib is administered at a dose of about 150 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein abemaciclib is administered at a dose of about 200 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein abemaciclib is administered at a dose of about 300 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein abemaciclib is administered at a dose of about 400 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein abemaciclib is administered as 50 mg, 100 mg, 150 mg, or 200 mg tablets. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein 150 mg of abemaciclib is administered tablets twice daily. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-

difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and abemaciclib, wherein 200 mg of abemaciclib is administered tablets twice daily.

5 In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and a MEK inhibitor.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein trametinib is administered at a dose in a range of about 1 mg to about 2 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein trametinib is administered at a dose of about 1 mg, when the subject is a pediatric patient with a body weight of about 26 kg to about 37 kg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein trametinib is administered at a dose of about 1.5 mg, when the subject is a pediatric patient with a body weight of about 38 kg to about 50 kg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein trametinib is administered at a dose of about 2 mg, when the subject is a pediatric patient with a body weight of about 51 kg or greater. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein trametinib is administered at a dose of about 2 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or

solvate thereof, and trametinib, wherein trametinib is administered as 0.5 mg or 2 mg tablets. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein 2 mg of trametinib is administered once daily. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein 1.5 mg of trametinib is administered once daily. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and trametinib, wherein 1 mg of trametinib is administered once daily.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein binimetinib is administered at a dose in a range of about 30 mg to about 90 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein binimetinib is administered at a dose of about 30 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein binimetinib is administered at a dose of about 45 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein binimetinib is administered at a dose of about 60 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein binimetinib is administered at a



dose of about 90 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein binimetinib is administered as 15 mg tablets. In some embodiments, the method comprises  
5 administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein 45 mg of binimetinib is administered as three 15 mg tablets twice daily. In some embodiments, the method comprises administering a crystalline form of  
10 (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and binimetinib, wherein 30 mg of binimetinib is administered as two 15 mg tablets twice daily.

In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib. In some embodiments,  
15 the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein palbociclib is administered at a dose in a range of about 75 mg to about 125 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein palbociclib is administered at a dose of about 75 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein palbociclib is  
25 administered at a dose of about 100 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein palbociclib is administered at a dose of about 125 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein palbociclib is  
30 administered at a dose of about 100 mg. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein palbociclib is

administered as 75 mg, 100 mg, or 125 mg tablets. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein 75 mg of palbociclib is administered once daily. In some  
5   embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein 100 mg of palbociclib is administered once daily. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and  
10   palbociclib, wherein 125 mg of palbociclib is administered once daily. In some embodiments, the method comprises administering a crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof, and palbociclib, wherein 125 mg of palbociclib is administered once daily  
15   as a 125 mg tablet.

## EXAMPLES

### Compound Preparation

The crystalline forms disclosed herein can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily  
20   prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or in light of the teachings herein. The synthesis of the compounds disclosed herein can be achieved by generally following the schemes provided herein, with modification for specific desired substituents. Methods for preparing the crystalline forms disclosed herein can be found in, e.g., PCT Published Application Number WO 2022/265993, filed on June 13, 2022; and  
25   Provisional Application Serial Number 63/532,695, filed on August 15, 2023; both of which are incorporated herein in their entirety.

### Methods

#### Polarized Light Microscopy (PLM):

The presence of crystallinity (birefringence) was determined using an Olympus BX50 microscope, equipped with cross-polarizing lenses and a Motic camera. Images were captured using Motic Images Plus 3.0. All images were recorded using the 20× objective, unless otherwise stated. The PLM image of Compound A prior to any crystallization trials (Form 1\*) is shown in FIG. 1, and FIG. 9 shows the PLM image Compound A, Form 1 after equilibration.

#### X-ray Powder Diffraction (XRPD):

XRPD analysis was carried out on a PANalytical X'pert pro with PIXcel detector (128 channels), scanning the samples between 3° and 35° 2θ. The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation ( $\alpha_1 \lambda = 1.54060 \text{ \AA}$ ;  $\alpha_2 = 1.54443 \text{ \AA}$ ;  $\beta = 1.39225 \text{ \AA}$ ;  $\alpha_1 : \alpha_2$  ratio = 0.5) running in transmission mode (step size 0.0130° 2θ, step time 18.87s) using 40 kV / 40 mA generator settings. XRPD analysis that used the longer basic batch method was carried out on a PANalytical X'pert pro with PIXcel detector (128 channels), scanning the samples between 3° and 35° 2θ. The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analyzed using Cu K radiation ( $\alpha_1 \lambda = 1.54060 \text{ \AA}$ ;  $\alpha_2 = 1.54443 \text{ \AA}$ ;  $\beta = 1.39225 \text{ \AA}$ ;  $\alpha_1 : \alpha_2$  ratio = 0.5) running in transmission mode (step size 0.0130° 2θ, step time 68.595s) using 40 kV / 40 mA generator settings. Data were visualized and images generated using the HighScore Plus 4.7 desktop application (PANalytical, 2017). Tables 14 - 18 list the peaks of the polymorphic forms of Compound A identified herein. The XRPD diffractogram of the initial Compound A prior to any crystallization trials is shown in FIG. 2, which was assigned to be Form 1\*. FIG. 4 and FIGS 5 - 8 show the long scan XRPD diffractograms of the polymorphic forms of Compound A identified herein.

#### Thermogravimetric Analysis/ Differential Scanning Calorimetry (TGA/DSC):

Material (3 – 10 mg of mg) was added into a pre-tared open aluminum pan and loaded into a TA Instruments Discovery SDT 650 Auto-Simultaneous DSC and held at room temperature. The sample was then heated at a rate of 10 °C/min from 30 – 400 °C during which time the change in

sample weight was recorded along with the heat flow response (DSC). Nitrogen was used as the sample purge gas, at a flow rate of 200 cm<sup>3</sup>/min.

Differential Scanning Calorimetry (DSC):

5           Material (1 – 5 mg) was weighed into an aluminum DSC pan and sealed non-hermetically with an aluminum lid. The sample pan was then loaded into a TA Instruments Discovery DSC 2500 differential scanning calorimeter equipped with a RC90 cooler. The sample and reference were heated to 210 °C at a scan rate of 10°C/min and the resulting heat flow response monitored. The sample was cooled to -80°C and then reheated again to 210 °C all at 10 °C/min. Nitrogen was  
10       used as the purge gas, at a flow rate of 50 cm<sup>3</sup>/min.

Karl Fischer Coulometric Titration (KF):

          Material (10 – 20 mg) was accurately weighed into a vial. The solid was then manually introduced into the titration cell of a Mettler Toledo C30 Compact Titrator. The vial was back-  
15       weighed after the addition of the solid and the weight of the added solid entered on the instrument. Titration was initiated once the sample had fully dissolved in the cell. The water content was calculated automatically by the instrument as a percentage.

Infrared Spectroscopy (IR):

20           Infrared spectroscopy was carried out on a Bruker ALPHA P spectrometer. Sufficient material was placed onto the center of the plate of the spectrometer and the spectra were obtained using the following parameters:

Resolution: 4 cm<sup>-1</sup>

Background Scan Time: 16 scans

25       Sample Scan Time: 16 scans

Data Collection: 4000 to 400 cm<sup>-1</sup>

Result Spectrum: Transmittance.

FIG. 10 shows the IR spectrum for Compound A

30       Nuclear Magnetic Resonance (NMR):

NMR experiments were performed on a Bruker AVIIIHD spectrometer equipped with a DCH cryoprobe operating at 500.12 MHz for protons. Experiments were performed in deuterated DMSO, and each sample was prepared to ca. 10 mM concentration. FIG. 11 and FIG. 12 show the  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra for compound A Form 1, respectively.

5

Dynamic Vapor Sorption (DVS):

Material (10 – 20 mg) was placed into a mesh vapor sorption balance pan and loaded into a DVS Intrinsic dynamic vapor sorption balance by Surface Measurement Systems. The sample was subjected to a ramping profile from 40 – 90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (dm/dt 0.004%, minimum step length 30 minutes, maximum step length 500 minutes) at 25°C. After completion of the sorption cycle, the sample was dried using the same procedure to 0% RH and then a second sorption cycle back to 40% RH. Two cycles were performed. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined. XRPD analysis was then carried out on any solid retained.

15

High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV):

Instrument: Dionex Ultimate 3000

Column: Waters X-Bridge C18 150 x 4.6mm 3.5 $\mu\text{m}$

20

Column Temperature: 35 °C

Autosampler Temperature: Ambient

UV wavelength: 220 nm

Injection Volume: 2  $\mu\text{L}$

Flow Rate: 1.0 mL/min

25

Mobile Phase A: 0.02% TFA in Deionised water

Mobile Phase B: 0.02% TFA in Acetonitrile

Gradient program:

| Time | Solvent A/ % | Solvent B /% |
|------|--------------|--------------|
| 0.0  | 80           | 20           |
| 1.0  | 80           | 20           |
| 15   | 5            | 95           |
| 17   | 5            | 95           |
| 17.1 | 80           | 20           |

|    |    |    |
|----|----|----|
| 25 | 80 | 20 |
|----|----|----|

**Example 1.** Initial characterization of Compound A.

The crystalline forms of Compound A described herein were initially characterized using a variety of techniques. Exemplary results of are described herein.

5

PLM analysis: As shown in FIG. 1, Compound A prior to crystallization appeared as small birefringent particles with a needle-like morphology.

XRPD: The diffractogram (FIG. 2) showed differences (circled) with a previous batch of Compound A; this new form was assigned as Form 1\*.

10 TG/DSC: The thermogram (FIG. 3) indicated multiple weight loss events prior to degradation, with a 2.5 % weight loss between 72 °C and 114 °C (theoretically equivalent to 0.5 moles of water), 2.2 % weight loss between 147 °C and 185 °C (theoretically equivalent to 0.5 moles of water) and a 12.2 % weight loss between 185 °C and 252 °C. There was an endothermic event at peak onset 86 °C (peak at 102 °C) associated with the first weight loss, followed by overlapping

15 endothermic events, the first with onset 154 °C (peak at 158 °C) and the second with onset 172 °C (peak at 176 °C), associated with the second weight loss. An endothermic event associated with degradation was observed with an onset of 294 °C (peak 301 °C).

HPLC purity: The batch used in all studies shown herein was determined to have an initial purity of 96.71 % area at 220 nM wavelength.

20

**Example 2.** Preparation and disproportionation assessment of Compound A mesylate saltProcedure A. Preparation of the mesylate salt

Approximately 1 g of Compound A was dissolved in 13.33 mL of ethyl acetate at 40 °C (concentration: 75 mg/mL). A solution of methane-sulfonic acid solution in ethyl acetate (2.87

25 mL of 1 M, 1.05 equivalents) was added then the solution was temperature cycled between 40 °C and 5 °C with a temperature ramp of 0.1 °C/min with a 1 hour hold between each step. After about 16 h of temperature cycling, a 700 µL subsample was taken (at 25 °C) from the resultant slurry, isolated via centrifugation, and analyzed by XRPD. The remaining solids were isolated via Buchner filtration at 5 °C.

30 Results:

5 XRPD analysis indicated Compound A mesylate salt to be crystalline (FIG. 13). TG/DSC analysis indicated one endothermic event with an onset temperature of 200 °C and a peak temperature of 207 °C (FIG. 14) and the <sup>1</sup>H NMR spectra indicated 1 equivalent of methane sulfonic acid.

5 Procedure B. Disproportionation assessment

The stability of Compound A mesylate salt was evaluated in three different buffer systems. For each assessment experiment, 250 mg of Compound A mesylate salt was suspended in 6.25 mL of buffer media with a pH of 1.2 (HCl/KCl), 4.5 (acetate buffer) and 6.8 (phosphate buffer). Each test solution was stirred at 37 °C for 24 hours and 700 µL samples were taken from the resultant slurries at 1, 2, 4, 6, and 24 hour time points. The solids were isolated via centrifugation and analyzed by XRPD. At each time point, the pH of the bulk samples was measured and adjusted to maintain the target pH.

10 Results:

XRPD analysis indicated that the mesylate salt disproportionated within 1 hour in all the three buffer media assessed (FIG. 15). The crystallinity of the solids recovered from the pH 4.5 and 6.8 buffer was significantly lower than that of the pH 1.2 buffer. These results indicate that Compound A mesylate salt has the potential to rapidly dissociate back to the parent species.

**Example 3. Preparation of Compound A amorphous form**

20 Procedure:

A stock solution of Compound A free base was prepared in 1,4-dioxane with a concentration of 40 mg/mL. This stock solution was aliquoted into 2 mL vials (500 µL per vial, corresponding to about 20 mg of Compound A per vial) and flash frozen at -40 °C. The flash frozen samples were lyophilized under vacuum for 3 days, then dried under vacuum at 40 °C for about 20 h.

25 Results:

The XRPD of lyophilized Compound A (FIG. 16) indicated the absence of crystallinity. The <sup>1</sup>H NMR spectrum indicated the presence of 0.02 mole equivalents of 1,4-dioxane in the amorphous solid.

30 **Example 4. Solvent solubility screen for amorphous form of Compound A**

Solvent solubility of the amorphous form of Compound A was assessed in order to aid the design of experimentation for a polymorph screen.

Procedure:

The appropriate solvent (see Table 3) was added to the about 20 mg lyophilized samples of Compound A in 20  $\mu$ L aliquots (1 volume) at ambient temperature until dissolution occurred or 2 mL of solvent had been added. Aliquot size was increased to 100  $\mu$ L (5 volumes) after 10 volumes were added without dissolution being observed. Gums were observed to form in the anisole and tBME experiments, solvent addition was discontinued after 1 mL. Experiments were heated to 40 °C between solvent additions to assess solubility at elevated temperatures. After dissolution, the solvent in the ethanol:water 95:5 % v/v, MIBK and THF experiments evaporated rapidly at 40 °C. XRPD analysis was performed on the resulting solids. Antisolvent was added to experiments that were clear solutions to generate slurries. All slurries were then temperature cycled for about 3 days between 40 °C and 5 °C with a temperature ramp of 0.1 °C/min and 1 hour holds between steps. After temperature cycling, solids were isolated via centrifugation and analyzed by XRPD (wet form). XRPD analysis was repeated after about 19 hours of drying under vacuum at ambient temperature (dry form).

**Table 3.** Solvent systems and XRPD results for the solvent solubility screen

| Solvent system <sup>y</sup> | Volume ( $\mu$ L) | Solubility   | Antisolvent/ Method <sup>z</sup> | Form (wet) | Form (dry) |
|-----------------------------|-------------------|--------------|----------------------------------|------------|------------|
| 1-Butanol                   | 100               | $\geq 200^x$ | heptane                          | 1          | 1          |
| 1-Propanol                  | 60                | $\geq 333^x$ | water                            | 1 (PC)     | 1 (PC)     |
| 2-Propanol:water 80:20      | 200               | $\geq 100^x$ | water                            | 1          | 1          |
| 2-Propanol:water 50:50      | 920               | $\geq 21^x$  | from slurry                      | 1          | 1          |
| 2-Methylpropan-1-ol         | 100               | $\geq 200$   | none                             | NS         | NS         |
| Acetone:water 80:20         | 80                | $\geq 250^x$ | water                            | 1          | 1          |
| Acetone:water 50:50         | 1320              | $\geq 15^x$  | water                            | 1          | 1          |
| Anisole                     | 1000              | $< 20$       | None (gum)                       | NS         | NS         |
| Butyl acetate               | 200               | $\geq 100^x$ | none                             | NS         | NS         |
| Dichloromethane             | 2000              | $< 10$       | from slurry                      | 3 (PC)     | AS         |
| Dimethylsulfoxide           | 60                | $\geq 333^x$ | water                            | 1 (PC)     | AS         |
| Ethanol:water 95:5          | 60                | $\geq 333^x$ | evaporation                      | 1          | 1          |
| Ethanol:water 75:25         | 400               | $\geq 50^x$  | water                            | 1          | 1          |
| Ethanol:water 50:50         | 2000              | $< 10$       | from slurry                      | 1          | 1          |
| Heptane                     | 2000              | $< 10$       | from slurry                      | 1          | 1          |
| Isopropyl acetate           | 120               | $\geq 166^x$ | none                             | NS         | NS         |
| Methanol:water 50:50        | 2000              | $< 10$       | from slurry                      | 1          | 1          |



|                                             |      |              |             |        |        |
|---------------------------------------------|------|--------------|-------------|--------|--------|
| Methylisobutyl ketone                       | 100  | $\geq 200^x$ | evaporation | 3 (PC) | 3 (PC) |
| t-ButylMethyl Ether                         | 1000 | $< 20$       | None (gum)  | NS     | NS     |
| Tetrahydrofuran                             | 60   | $\geq 333^x$ | evaporation | 3 (PC) | 3 (PC) |
| iPrOAc:heptane 22:78                        | 2000 | $< 10$       | from slurry | 3 (PC) | 3 (PC) |
| iPrOAc:heptane:water 21:78:1                | 2000 | $< 10$       | from slurry | 1*     | 1*     |
| iPrOAc:heptane:acetonitrile 21:78:1         | 2000 | $< 10$       | from slurry | 1*     | 1*     |
| iPrOAc:heptane:acetonitrile:water 20:78:1:1 | 2000 | $< 10$       | from slurry | 1*     | 1*     |

<sup>x</sup>dissolved at 40 °C; <sup>y</sup>numerical values refer to % by volume; <sup>z</sup>method to obtain solid; PC = poorly crystalline; NS = no solids obtained; AS = amorphous solid

### Results:

As shown in Table 3, high solubility ( $\geq 200$  mg/mL) was observed in 1-butanol, 1-propanol, 2-methylpropan-1-ol, acetone:water 80:20 % v/v, dimethyl sulfoxide (DMSO), ethanol:water 95:5 % v/v, methylisobutyl ketone (MIBK) and tetrahydrofuran (THF). Moderate solubility (100 – 200 mg/mL) was observed in 2-propanol:water 80:20 % v/v, butyl acetate and isopropyl acetate. Low solubility (10 – 50 mg/mL) was observed in 2-propanol:water 50:50 % v/v, acetone:water 50:50 % v/v and ethanol:water 75:25 % v/v ( $\geq 50$  mg/mL). Very low solubility ( $< 10$  mg/mL) was observed in dichloromethane, ethanol:water 50:50 % v/v, heptane, methanol:water 50:50 % v/v and the process relevant isopropyl acetate:heptane mixtures.

Solids were recovered from 19 of the 24 experiments (after addition of antisolvent and subsequent temperature cycling); XRPD analysis showed most of the samples to be consistent with Form 1. Form 1 was recovered from the process relevant isopropyl acetate:heptane mixtures. Form 3, was recovered from dichloromethane, methylisobutyl ketone, tetrahydrofuran and isopropyl acetate:heptane 22:78 % v/v. After drying, the solids recovered from dichloromethane became amorphous.

### **Example 5. Primary polymorph screen of Compound A**

To identify potential additional polymorphic forms of Compound A and the conditions under which they can be generated, a polymorph screen was carried out. Crystallization techniques including evaporation, temperature cycling, antisolvent addition, slow cooling and solvent drop grinding were explored.

#### Procedure A. Evaporation:

The appropriate solvent (see Table 4) was added to 20 mg samples of amorphous Compound A in 20  $\mu$ L aliquots at ambient temperature until dissolution was observed or 500  $\mu$ L had been added. Where 500  $\mu$ L was added, complete dissolution was not observed. The experiments were evaporated at ambient temperature. After approximately 4 days, the resulting solids were analyzed by XRPD, dried for about 18 h under vacuum at 40  $^{\circ}$ C, then reanalyzed by XRPD.

**Table 4.** Solvent systems and XRPD results for primary polymorph screen, Procedure A

| Solvent system <sup>x</sup>                             | Volume ( $\mu$ L) | Form (wet) | Form (dry) |
|---------------------------------------------------------|-------------------|------------|------------|
| 1-Butanol                                               | 160               | 1*         | 1*         |
| 1-Propanol:water 50:50                                  | 500               | 1          | 1          |
| 2-Propanol:water 80:20                                  | 200               | 1          | 1          |
| 2-methyl-1-propanol:heptane 70:30                       | 200               | 1          | 1          |
| Acetone:water 70:30                                     | 100               | 1          | 1          |
| Acetonitrile:water 95:5                                 | 200               | 1*         | 1*         |
| Butyl acetate                                           | 200               | 3 (PC)     | 3 (PC)     |
| Dichloromethane                                         | 500               | 3 (PC)     | 3 (PC)     |
| Dimethyl sulfoxide:water 80:20                          | 120               | NS         | NS         |
| Ethanol                                                 | 100               | 1          | 1          |
| Ethanol:water 80:20                                     | 200               | 1          | 1          |
| Ethyl acetate                                           | 300               | 3 (PC)     | 3 (PC)     |
| Isopropyl acetate                                       | 180               | 3 (PC)     | 3 (PC)     |
| Isopropyl acetate:heptane 70:30                         | 400               | 3 (PC)     | 3 (PC)     |
| Isopropyl acetate:heptane :acetonitrile:water 68:30:1:1 | 400               | 3 (PC)     | 3 (PC)     |
| Methanol:water 80:20                                    | 200               | 1          | 1          |
| Methylisobutyl ketone                                   | 200               | 3 (PC)     | 3 (PC)     |
| Tetrahydrofuran                                         | 100               | 3 (PC)     | 3 (PC)     |

<sup>x</sup>numerical values refer to % by volume; NS = no solids obtained; PC = poorly crystalline

### Results:

As shown in Table 2, XRPD analysis of the seventeen recovered solids indicated seven were consistent with Form 1, two were consistent with Form 1\*, and eight were consistent with Form 3. While 1-butanol and acetonitrile: water 95:5 gave Form 1\*, propanol/water mixtures gave Form 1 (FIG. 17). Form 3 was observed to form in organic solvents systems isopropyl acetate:heptane 70:30, methyl isopropyl ketone, and tetrahydrofuran, while methanol:water 80:20

gave Form 1 (FIG. 18). No significant changes were observed by XRPD after drying. Complete evaporation was not observed in the DMSO:water 80:20 % v/v experiment.

*Procedure B. Temperature cycling:*

The appropriate solvent (see Table 5) was added to 20 mg samples of amorphous Compound A in 20  $\mu$ L aliquots at 40 °C to form slurries. The experiments were temperature cycled between 40 °C and 5 °C with a ramp of 0.1 °C/min and 1 h hold between steps. After approximately 4 days of temperature cycling, the experiments were cooled from 40 °C to 5 °C over 2 h. The resulting solids were analyzed by XRPD, dried for about 18 h under vacuum at 40 °C, then reanalyzed by XRPD.

**Table 5.** Solvent systems and XRPD results for primary polymorph screen, Procedure B

| Solvent system <sup>x</sup>                            | Volume ( $\mu$ L) | Form (wet)  | Form (dry) |
|--------------------------------------------------------|-------------------|-------------|------------|
| 1-Butanol                                              | 60                | 1           | 1          |
| 1-Propanol:water 50:50                                 | 60                | 1           | 1          |
| 2-Propanol:water 80:20                                 | 60                | 1           | 1          |
| 2-methyl-1-propanol:heptane 70:30                      | 100               | 1           | 1          |
| Acetone:water 70:30                                    | 60                | 1           | 1          |
| Acetonitrile:water 95:5                                | 80                | 1*          | 1*         |
| Butyl acetate                                          | 60                | 3 (PC)      | 3 (PC)     |
| Dichloromethane                                        | 1000              | 3 (PC)      | 3 (PC)     |
| Dimethyl sulfoxide:water 80:20                         | 40                | NS          | NS         |
| Ethanol                                                | 40                | NS          | NS         |
| Ethanol:water 80:20                                    | 60                | 3 (PC)      | 3 (PC)     |
| Ethyl acetate                                          | 60                | AS          | AS         |
| Isopropyl acetate                                      | 60                | 1           | 1          |
| Isopropyl acetate:heptane 70:30                        | 100               | 1* & 3 (PC) | 3 (PC)     |
| Isopropyl acetate:heptane:acetonitrile:water 68:30:1:1 | 100               | 1*          | 1*         |
| Methanol:water 80:20                                   | 100               | 1           | 1          |
| Methylisobutyl ketone                                  | 100               | 1*          | 1*         |
| Tetrahydrofuran                                        | 40                | NS          | NS         |

<sup>x</sup>numerical values refer to % by volume; NS = no solids obtained; PC = poorly crystalline; AS = amorphous solid

*Results:*

As shown in Table 5, XRPD analysis of the fifteen recovered solids indicated seven were consistent with Form 1, three were consistent with Form 1\*, and three were consistent with Form

3. Amorphous solids were recovered from ethyl acetate. A mixture of Form 1\* and Form 3 was recovered from the isopropyl acetate:heptane 70:30 % v/v. After drying under vacuum at 40 °C for about 18 h, the solids recovered from the isopropyl acetate:70:30 % v/v experiment became consistent with Form 3. No other significant changes were observed post-drying.

5 Procedure C. Antisolvent addition:

The appropriate solvent (see Table 6) was added to 20 mg samples of amorphous Compound A in 20 µL aliquots at ambient temperature (about 20 °C) until dissolution was observed or 500 µL was added. Antisolvent was added to the solutions until precipitation or some other change (e.g. gumming or oiling) was observed. The resulting slurries were isolated via centrifugation (where volume permitted) and the solids were analyzed by XRPD, dried for  
10 approximately 18 h under vacuum at 40 °C, then reanalyzed by XRPD.

Complete dissolution was not observed in the 1-propanol:water 50:50 % v/v experiment after the addition of 500 µL at 20 °C.

15 **Table 6.** Solvent systems and XRPD results for primary polymorph screen, Procedure C

| Solvent System <sup>x</sup>                             | Anti-solvent | Volume added (µL) |                | Form (wet) | Form (dry) |
|---------------------------------------------------------|--------------|-------------------|----------------|------------|------------|
|                                                         |              | Solvent           | Antisolvent    |            |            |
| 1-Butanol                                               | Heptane      | 200               | 1500           | 3 (PC)     | 1          |
| 1-Propanol:water 50:50                                  | Water        | 500               | 0              | 1          | 1 (PC)     |
| 2-Propanol:water 80:20                                  | Water        | 300               | 300            | 1          | 1          |
| 2-methyl-1-propanol:heptane 70:30                       | Heptane      | 200               | 300            | 1 (PC)     | 1          |
| Acetone:water 70:30                                     | Water        | 200               | 0 <sup>y</sup> | 1*         | 1*         |
| Acetonitrile:water 95:5                                 | Water        | 100               | 0 <sup>y</sup> | 1*         | 1*         |
| Butyl acetate                                           | Heptane      | 200               | 100            | AS         | 1*         |
| Dimethyl sulfoxide:water 80:20                          | Water        | 300               | 200            | 1 (PC)     | 1          |
| Ethanol                                                 | Water        | 100               | 100            | 1 (PC)     | 1          |
| Ethanol:water 80:20                                     | Water        | 100               | 0 <sup>y</sup> | 1          | 1          |
| Ethyl acetate                                           | Heptane      | 200               | 300            | 3 (PC)     | 3 (PC)     |
| Isopropyl acetate                                       | Heptane      | 200               | 300            | 3 (PC)     | AS         |
| Isopropyl acetate:heptane 70:30                         | Heptane      | 400               | 240            | 3 (PC)     | 3 (PC)     |
| Isopropyl acetate:heptane :acetonitrile:water 68:30:1:1 | Heptane      | 400               | 260            | 3 (PC)     | 1          |
| Methanol:water 80:20                                    | Water        | 200               | 0 <sup>y</sup> | 1          | 1          |
| Methylisobutyl ketone                                   | Heptan       | 100               | 100            | AS         | 1          |
| Tetrahydrofuran                                         | Water        | 100               | 200            | 1          | 1          |

<sup>x</sup>numerical values refer to % by volume; <sup>y</sup>Precipitation observed before antisolvent addition; PC = poorly crystalline; AS = amorphous solid

### Results:

As shown in Table 6, XRPD analysis of the thirteen recovered solids prior to cooling to 5 °C indicated seven were consistent with Form 1, two were consistent with Form 1\*, and four were consistent with Form 3. The experiments that yielded oil or gum were cooled from 25 °C to 5 °C at 0.1 °C/min and held at 5 °C for about 19 h. Conversion to slurries was observed in all the experiments; these were isolated via centrifugation and analyzed by XRPD. The solids isolated from the 1-butanol experiment were consistent with Form 3, the solids from the 2-methyl-1-propanol:heptane 70:30 were consistent with Form 1.

### Procedure D. Slow cooling:

The appropriate solvent (see Table 7) was added to 20 mg samples of amorphous Compound A in 20 µL aliquots at 40 °C until dissolution was observed or 1000 µL was added. The experiments were cooled from 40 °C to 5 °C at 0.05 °C/min. After about 60 h at 5 °C, the resulting slurries were isolated via centrifugation and the solids were analyzed by XRPD, dried for about 18 h under vacuum at 40 °C, then reanalyzed by XRPD. Samples that were clear solutions at 5 °C were stored at -20 °C for c.a. 4 days. Where required, antisolvent was added in 100 µL aliquots to the experiments removed from storage at -20 °C until precipitation, gumming or oiling was observed.

**Table 7.** Solvent systems and XRPD results for primary polymorph screen, Procedure D

| Solvent System <sup>x</sup>       | Vol. solvent system (µL) | Anti-solvent | Vol. anti-solvent (µL) | Form (wet) | Form (dry) |
|-----------------------------------|--------------------------|--------------|------------------------|------------|------------|
| 1-Butanol                         | 100                      | Heptane      | 300                    | 1*         | 1*         |
| 1-Propanol:water 50:50            | 1000                     | none         | N/A                    | 1          | 1          |
| 2-Propanol:water 80:20            | 300                      | Water        | 100                    | 1          | 1          |
| 2-methyl-1-propanol:heptane 70:30 | 200                      | none         | N/A                    | 1* (PC)    | 1* (PC)    |
| Acetone:water 70:30               | 200                      | none         | N/A                    | 1          | 1          |
| Acetonitrile:water 95:5           | 100                      | none         | N/A                    | 1*         | 1*         |
| Butyl acetate                     | 200                      | Heptane      | 300                    | Gum        | Gum        |
| Dimethyl sulfoxide:water 80:20    | 300                      | Water        | 200                    | 1 (PC)     | AS         |
| Ethanol                           | 80                       | Water        | 200                    | 1 (PC)     | 1          |
| Ethanol:water 80:20               | 500                      | none         | N/A                    | 1          | 1          |
| Ethyl acetate                     | 200                      | Heptane      | 500                    | 3 (PC)     | 1* (PC)    |

|                                                            |     |         |     |     |     |
|------------------------------------------------------------|-----|---------|-----|-----|-----|
| Isopropyl acetate                                          | 180 | Heptane | 300 | Gum | Gum |
| Isopropyl acetate:heptane 70:30                            | 400 | none    | N/A | AS  | AS  |
| Isopropyl acetate:heptane<br>:acetonitrile:water 68:30:1:1 | 400 | none    | N/A | 1*  | 1*  |
| Methanol:water 80:20                                       | 500 | none    | N/A | 1   | 1   |
| Methylisobutyl ketone                                      | 200 | Heptane | 300 | Gum | Gum |
| Tetrahydrofuran                                            | 100 | Water   | 200 | Gum | Gum |

<sup>a</sup>numerical values refer to % by volume; N/A = not applicable; PC = poorly crystalline; AS = amorphous solid

### Results:

5 As shown in Table 7, XRPD analysis of the nine solids recovered prior to storage at -20 °C and antisolvent addition indicated four were consistent with Form 1, three were consistent with Form 1\*, and one was consistent with Form 3. One condition gave a gum and one an amorphous solid. Storage at -20 °C and subsequent antisolvent addition allowed for the recovery of solids from 2-propanol:water, DMSO:water, ethanol and ethyl acetate. The solid sample recovered from ethyl acetate was Form 3; the other samples were consistent with Form 1. After drying under vacuum at 40 °C for about 18 h, the solids recovered from the dichloromethane experiment dried to Form 1. The DMSO:water 80:20 % v/v solids became amorphous. The ethyl acetate solids became Form 1\*.

### Procedure E. Solvent drop grinding:

15 20 µL of the appropriate solvent (see Table 8) was added to 20 mg samples of amorphous Compound A in 2 mL milling tubes, along with two stainless steel beads. The experiments were milled with the following parameters: 5000 RPM, 10 × 90 second cycles with 10 second holds between cycles. The milling was carried out four times, and resulting solids were analyzed by XRPD, dried for about 18 h under vacuum at 40 °C, then reanalyzed by XRPD.

20 **Table 8.** Solvent systems and XRPD results for primary polymorph screen, Procedure E

| Solvent System <sup>x</sup>       | XRPD (wet) | XRPD (dry)  |
|-----------------------------------|------------|-------------|
| 1-Butanol                         | NS         | NS          |
| 1-Propanol:water 50:50            | Form 1     | Form 1      |
| 2-Propanol:water 80:20            | Form 1     | Form 1      |
| 2-methyl-1-propanol:heptane 70:30 | NS         | NS          |
| Acetone:water 70:30               | Form 1     | Form 1      |
| Acetonitrile:water 95:5           | AS         | Form 1*(PC) |
| Butyl acetate                     | NS         | NS          |
| Dichloromethane                   | Form 1(PC) | Form 1      |
| Dimethyl sulfoxide:water 80:20    | NS         | NS          |

|                                                         |                         |                |
|---------------------------------------------------------|-------------------------|----------------|
| Ethanol                                                 | NS                      | NS             |
| Ethanol:water 80:20                                     | Form 1(PC)              | Form 1(PC)     |
| Ethyl acetate                                           | NS                      | NS             |
| Isopropyl acetate                                       | NS                      | NS             |
| Isopropyl acetate:heptane 70:30                         | NS                      | NS             |
| Isopropyl acetate:heptane :acetonitrile:water 68:30:1:1 | Form 3(PC) <sup>z</sup> | Form 1*/ 3(PC) |
| Methanol:water 80:20                                    | Form 1                  | Form 1         |
| Methylisobutyl ketone                                   | NS                      | NS             |
| Tetrahydrofuran                                         | Form 3(PC)              | Form 1         |

<sup>x</sup>numerical values refer to % by volume; PC = poorly crystalline; NS = no solid; AS = amorphous solid;  
<sup>z</sup> = extra peaks detected

### Results:

As shown in Table 8, solids were recovered from 9 of the 18 solvent drop grinding experiments. XRPD analysis indicated: 6 forms were consistent with Form 1, 2 were consistent with Form 3, and 1 was predominantly amorphous. After drying under vacuum at 40 °C for about 18 h, the solids recovered from the dichloromethane experiment became more crystalline and the Isopropyl acetate:heptane: acetonitrile:water 68:30:1:1 % v/v/v/v converted to a mixture of Form 1\* and Form 3.

### **Example 6.** Solubility assessment of Compound A Form 1\*

While solubility experiments were carried out on the amorphous form of Compound A (see **Example 4**), the solubility of the initial form of Compound A (assigned as Form 1\*) also required evaluation.

### Procedure:

Received Compound A (Form 1\*) was weighed out (about 20 mg per vial) into 2 mL vials, then solvent (see Table 9) was added in 20 µL aliquots at 50 °C until dissolution was observed.

**Table 9.** Results from the solubility assessment of Compound A Form 1\*

| Solvent    | Volume added (µL) | Solubility (mg/mL) at 50 °C |
|------------|-------------------|-----------------------------|
| 1-propanol | 200               | 100-111                     |
| 2-propanol | 160               | 125-143                     |
| Acetone    | 200               | 100-111                     |
| Ethanol    | 200               | 100-111                     |
| Methanol   | 200               | 100-111                     |

Results:

As shown in Table 9, the solubility of Compound A Form 1\* ranged from 100 to 111 mg/mL in 1-propanol, acetone, ethanol and methanol, and from 125 to 143 mg/mL in 2-propanol.

5

**Example 7.** Chemical stability of Compound A in test solvents

Solution chemical stability was assessed in MeOH and EtOH with the potential dissolution point from the view of process design. Purity was assessed by HPLC with monitoring at 252 nM.

10 **Table 10.** Chemical stability of compound A

| Retention time/min | MeOH (25°C, 200 mg/mL) |               |               | EtOH (50°C, 250 mg/mL) |               |               | EtOH (25 °C 83.3 mg/mL) |               |               |
|--------------------|------------------------|---------------|---------------|------------------------|---------------|---------------|-------------------------|---------------|---------------|
|                    | 0 h                    | 6 h           | 24 h          | 0 h                    | 5 h           | 24 h          | 0 h                     | 6 h           | 24 h          |
| 0.86               | 0.04%                  | 0.04%         | 0.04%         | 0.03%                  | 0.04%         | 0.04%         | 0.03%                   | 0.04%         | 0.04%         |
| 0.89               | -                      | -             | 0.02%         | 0.03%                  | 0.03%         | 0.03%         | -                       | -             | -             |
| <b>1.00</b>        | <b>95.14%</b>          | <b>95.21%</b> | <b>95.16%</b> | <b>95.37%</b>          | <b>95.16%</b> | <b>94.77%</b> | <b>95.29%</b>           | <b>95.37%</b> | <b>95.34%</b> |
| 1.08               | 0.61%                  | 0.61%         | 0.61%         | 0.61%                  | 0.64%         | 0.69%         | 0.61%                   | 0.59%         | 0.59%         |
| 1.13               | 0.08%                  | 0.08%         | 0.08%         | 0.07%                  | 0.08%         | 0.08%         | 0.07%                   | 0.07%         | 0.07%         |
| 1.59               | 0.04%                  | -             | 0.04%         | 0.04%                  | 0.05%         | 0.05%         | 0.04%                   | 0.04%         | 0.04%         |
| 1.63               | 4.04%                  | 4.02%         | 4.02%         | 3.80%                  | 3.97%         | 4.30%         | 3.91%                   | 3.85%         | 3.87%         |
| 1.68               | 0.05%                  | 0.05%         | 0.05%         | 0.04%                  | 0.05%         | 0.05%         | 0.05%                   | 0.04%         | 0.04%         |

Results:

As shown in Table 10, some degradation was observed in EtOH at 50 °C, particularly after 24 h. The chemical stability at 25 °C remained high in both solvents.

15

**Example 8.** Crystallization in aqueous methanol and ethanol

Two preliminary crystallization experiments were performed in MeOH/H<sub>2</sub>O and EtOH/H<sub>2</sub>O.

Procedure A. Crystallization:

20

Compound A (5 g) was dissolved in 25 mL (5 V) MeOH) at 25 °C and 40 mL (8 V) EtOH at 50 °C, respectively. Then a small amount of water was charged into the system to make a supersaturated solution. The temperature was adjusted to 20-25 °C and 2 % seed (Form 1) was added, followed by aging and anti-solvent addition to finish the crystallization.



**Table 11.** Preliminary crystallization experiments in MeOH/H<sub>2</sub>O and EtOH/H<sub>2</sub>O

| Dissolution |      | Seeding                           |      |        |        | Anti-solvent addition |        | Form | Purity % | H <sub>2</sub> O % | MeOH % |
|-------------|------|-----------------------------------|------|--------|--------|-----------------------|--------|------|----------|--------------------|--------|
| Solvent     | T/°C | Solvent                           | T/°C | Load/% | Time/h | H <sub>2</sub> O Vol  | Time h |      |          |                    |        |
| MeOH<br>5v  | 25   | MeOH/H <sub>2</sub> O<br>5v/0.07v | 25   | 2      | 1      | 1.18v                 | 8      | 1    | 95.8     | 2.2                | 0.16   |
| EtOH<br>8v  | 50   | EtOH/H <sub>2</sub> O<br>8v/0.04v | 20   | 2      | 1      | 3.96v                 | 6      | 1    | 97.5     | 2.2                | 0.22   |

Results:

As shown in Table 11, both of the above Procedure A experiments generated Form 1 (see FIGs 19 and 20), and the amount of residual solvents met ICH guidelines. It was observed that mother liquor assay was high as well for the experiment that generated high purity product.

Procedure B: Form 1 purity evaluation:

In order to verify whether there was a relationship between Form 1 purity and mother liquor loss, a group of slurry experiments in the same solvent composition was carried out with different volumes. Purity of residual solids was assessed and mother liquor loss was calculated.

**Table 12.** Impurity purging study in MeOH/H<sub>2</sub>O system

| Input                       | Solvent            | Volume/v | T/°C | Results |                     |
|-----------------------------|--------------------|----------|------|---------|---------------------|
|                             |                    |          |      | Purity  | Loss in supernatant |
| Compound A<br>Purity: 95.5% | MeOH/<br>water 4/1 | 5        | 25   | 95.8%   | 9.4%                |
|                             |                    | 6.25     |      | 95.9%   | 11.3%               |
|                             |                    | 10       |      | 96.0%   | 17.5%               |
|                             |                    | 15       |      | 96.7%   | 26.0%               |
|                             |                    | 20       |      | 98.9%   | 34.9%               |
|                             |                    | 30       |      | 99.2%   | 54.9%               |
|                             |                    | 40       |      | 99.3%   | 65.8%               |
|                             |                    | 50       |      | 99.3%   | 83.9%               |

Results:

Based on the results shown in Table 12 shown above, 6.25 volumes of solvent mixture 4:1 MeOH/H<sub>2</sub>O did not result in removal of impurities.

*Procedure C. Form 1 stability upon drying:*

Drying stability of Form 1 obtained from crystallization in MeOH/water was carried out to determine if residual methanol could be reduced.

**Table 13.** Drying stability of Form 1

| Input        | T/°C | Time/h                      |                              |                             |                                                       |
|--------------|------|-----------------------------|------------------------------|-----------------------------|-------------------------------------------------------|
|              |      | 18                          | 24                           | 42                          | 66                                                    |
| Form 1 (wet) | 40   | Purity: 95.8%<br>MeOH:0.18% | Purity: 95.8%<br>MeOH: 0.17% | Purity:95.9%<br>MeOH: 0.17% | Purity: 95.9%<br>MeOH: 0.16%<br>H <sub>2</sub> O:2.2% |

*Results:*

As shown in Table 13, residual methanol did not change significantly when prolonging the drying time, which suggests the solvent is incorporated into the crystal lattice. The water content did not change with drying either, which demonstrates the hemi hydrate is stable.

**Example 9.** Crystallization process optimization

Crystallization experiments designed around the preliminary crystallization study results (**Example 8**) all yielded Form 1. The protocols are listed herein, and the conditions and analytical results are shown in Table 14.

*Procedure A. Crystallization in MeOH/Water:* Compound A was dissolved in 10 V MeOH and then 0.5 V H<sub>2</sub>O was added, followed by seed addition and 1 h aging. After that, 4.5 V H<sub>2</sub>O was dosed over 8 h. Experiment A resulted in Form 1 in 94.9 % yield. Residual methanol in the dried product was 0.14 % and water content by Karl Fischer titration was 2.2 %.

*Procedure B. Effect of reduced seed particle size:* Form 1 seed was ground with a mortar and pestle, and added at step 5 (see Procedure B and Table 14 below). The analytical data from Procedure B was comparable to those obtained from Procedure A, but the residual methanol in the dried product was significantly reduced (831 ppm).

*Procedure C. Effect of reduced the seed loading:* Similar to Procedure A, except that 0.5% ground seed into reactor in step 5. Residual methanol was a little higher for the dried product (Form 1) obtained with Procedure C relative to the other Procedures.

Procedure D. Effect on crystallization phenomenon and product quality without seeding: The results for Experiment D indicated that crystallization occurred upon water addition with good product quality for Form 1.

Procedure A:

- 5 1. Charged Compound A (5.05 g) into reactor.
2. Charged 10v MeOH (50 mL) into reactor.
3. Stirred contents of reactor for 1 h at 20 °C.
4. Charged 0.5v (H<sub>2</sub>O 2.5 mL ) into reactor.
5. Charged 2% seed into reactor.
- 10 6. Stirred contents of reactor for 1 h at 20 °C.
7. Charged 4.5v H<sub>2</sub>O (22.5 mL) into the reactor dropwise over 8 h.
8. Stirred contents of reactor for 12 h at 20 °C.
9. Took wet solid to check XRPD.
10. Took mother liquid to check by HPLC.
- 15 11. Filtered contents of reactor.
12. Rinsed wet cake with 2v MeOH/H<sub>2</sub>O 2/1 (10 mL).
13. Dried the wet cake at 40 °C for 22 h.
14. Obtained crystalline form of Compound A.

20 Procedure B:

1. Charged Compound A (5.05 g) into reactor.
2. Charged 10v MeOH (50 mL) into reactor.
3. Stirred contents of reactor for 0.5 h at 20 °C.
4. Charged 0.5v (H<sub>2</sub>O 2.5 mL ) into reactor.
- 25 5. Charged 2% ground seed into reactor.
6. Stirred contents of reactor for 1 h at 20 °C.
7. Charged 4.5v H<sub>2</sub>O (22.5 mL) into the reactor dropwise over 8 h.
8. Stirred contents of reactor for 12 h at 20 °C.
9. Filtered contents of reactor.
- 30 10. Rinsed wet cake with 2v MeOH/H<sub>2</sub>O 2/1 (10 mL).
11. Dried the wet cake at 40 °C for 20 h.
12. Obtained crystalline form of Compound A.

Procedure C:

- 35 1. Charged Compound A (5.05 g) into reactor.
2. Charged 10v MeOH (50 mL) into reactor.
3. Stirred contents of reactor for 0.5 h at 20 °C.
4. Charged 0.5v (H<sub>2</sub>O 2.5 mL ) into reactor.
5. Charged 0.5% ground seed into reactor.
- 40 6. Stirred contents of reactor for 1 h at 20 °C.
7. Charged 4.5v H<sub>2</sub>O (22.5 mL) into the reactor dropwise over 8 h.
8. Stirred contents of reactor for 13 h at 20 °C.
9. Filtered contents of reactor.
10. Rinsed wet cake with 2v MeOH/H<sub>2</sub>O 2/1 (10 mL).

11. Dried the wet cake at 40 °C for 20 h.
12. Obtained crystalline of Compound A.

Procedure D:

- 5 1. Charged Compound A (5.05 g) into reactor.
2. Charged 10v MeOH (50 mL) into reactor.
3. Stirred contents of reactor for 0.5 h at 20 °C.
4. Charged 0.5v (H<sub>2</sub>O 2.5 mL) into reactor.
5. Stirred contents of reactor for 4 h at 20 °C.
- 10 6. Charged 4.5v H<sub>2</sub>O (22.5 mL) into the reactor dropwise over 8 h.
7. Stirred contents of reactor for 9 h at 20 °C.
8. Filtered contents of reactor.
9. Rinsed wet cake with 2v MeOH/H<sub>2</sub>O 2/1 (10 mL).
- 10 10. Dried the wet cake at 40 °C for 22 h.
- 15 11. Obtained crystalline of Compound A.

**Table 14.** Crystallization optimization in MeOH/H<sub>2</sub>O

| Protocol* | Dissolution |      | Seeding                           |      |       |      | Anti-solvent addition    |      | Results                                                    |
|-----------|-------------|------|-----------------------------------|------|-------|------|--------------------------|------|------------------------------------------------------------|
|           | Solvent     | T/°C | Solvent                           | T/°C | Load% | Time | Solvent                  | Time |                                                            |
| A         | MeOH<br>10v | 20   | MeOH/H <sub>2</sub> O<br>10v/0.5v | 20   | 2     | 1 h  | H <sub>2</sub> O<br>4.5v | 8 h  | Purity: 95.4%<br>ML loss: 5%<br>KF: 2.2%<br>MeOH: 0.14%    |
| B         | MeOH<br>10v | 20   | MeOH/H <sub>2</sub> O<br>10v/0.5v | 20   | 2**   | 1h   | H <sub>2</sub> O<br>4.5v | 8 h  | Purity: 95.5%<br>ML loss: 5.3%<br>KF: 2.3%<br>MeOH: 831ppm |
| C         | MeOH<br>10v | 20   | MeOH/H <sub>2</sub> O<br>10v/0.5v | 20   | 0.5%  | 1h   | H <sub>2</sub> O<br>4.5v | 8 h  | Purity: 95.3%<br>ML loss: 5.4%<br>KF: 2.2%<br>MeOH: 0.2%   |
| D         | MeOH<br>10v | 20   | MeOH/H <sub>2</sub> O<br>10v/0.5v | 20   | N/A   | 4 h  | H <sub>2</sub> O<br>4.5v | 8 h  | Purity: 95.5%<br>ML loss: 5.3%<br>KF: 2.3%<br>MeOH: 0.17%  |

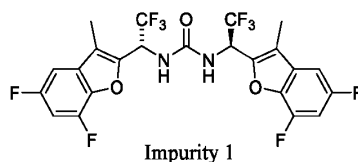
\*each protocol used 5 g Compound A (95.5% purity); \*\*Ground seeds; ML=mother liquor; KF = Karl Fischer (% w/w water content); N/A = not applicable

20

Results:

As shown in Table 14, protocols A, B, C, and D all produced Compound A Form 1 in high purity with no evidence of the presence of a known impurity (Impurity 1, 1,3-bis((R)-1-

(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, shown below) that arises during synthesis of Compound A as evidenced by XRPD analysis (see FIGS. 19-24).



5 **Example 10.** Manufacturing protocols for Compound A Form 1.

Procedure A:

The intermediate product was dissolved in methanol (6.3 wt eq) at 20–30 °C before being polish-filtered through a 0.2-micron filter followed by a reactor rinse (1.6 wt eq). The batch was cooled to 15–25 °C before purified water (0.5 wt eq) was added via a 0.2-micron filter followed by addition of Compound A Form 1 seed (0.01 wt eq). The mixture was agitated at 15–25 °C for approximately 3 hours before purified water (4.5 wt eq) was added via a 0.2-micron filter over a period of approximately 8 hours. The batch was agitated 15–25 °C for approximately 16 hours to effect crystallization completion. The batch was filtered and washed with a pre-mixed solution of methanol (1.1 wt eq) and purified water (0.7 wt eq) via a 0.2-micron filter. Product was dried at 35–45 °C under vacuum with nitrogen sweep for at least 24 hours until constant weight and IPC indicates water content of 2.0–2.6 wt%. Compound A Form 1 (XRPD shown in FIG. 4) is discharged to double LDPE liner-bags in a HDPE drum.

Procedure B:

The intermediate product (13.11 kg) was dissolved in MeOH (74.2 kg) followed by polish filtration using an in-line cartridge filter in which another 18.6 kg MeOH was used as a rinse. To this MeOH solution was added 4.41 kg water and then 115.9 g of Compound A hemi-hydrate Form 1 seeds. The resulting mixture was agitated at 20°C for 3 hours and water (53.32 kg) was slowly added over 8 hours to maximize the yield. After agitating at 20°C overnight (17 hours), the solid was filtered in the filter-dryer and the filter cake was washed with a pre-mixed 20.4 kg MeOH:water (2:1). The wet cake was dried under vacuum with a nitrogen bleed and intermittent agitation at the jacket temperature of 40°C for 45 hours to afford 10.87 kg Compound A, hemi-hydrate Form 1 with a UPLC purity of 99.9 % (peak area), assay of 100.4 % (w/w) and HPLC chiral purity of 100.0 (peak area or ee).

*Procedure C:*

The intermediate product (2.5 g) was dissolved in 20 mL (8 vol.) of 2-propanol at 50 °C in a 100 mL temperature-controlled reactor. Once dissolved, the mixture was cooled to 40 °C at 1 °C/min. At 40 °C, 80 mL (32 vol.) of water was added to the mixture at 5 mL/h (2 vol. per hour). After 5  
antisolvent addition was complete, the mixture was cooled to 5 °C at 0.2 °C/min. The mixture was temperature cycled between 5 °C and 40 °C with a temperature ramp of 0.1 °C/min and 1 hour holds between steps for 1 cycle before returning to 5 °C. After about 11 h at 5 °C, the experiment was isolated via Buchner filtration and analyzed by XRPD. The isolated solids were dried under vacuum at 40 °C for about 18 h, then under vacuum at ambient temperature for a 10  
further 65 h. Note: over-drying of the product gives Form 4, which reverts to Form 1 upon storage in ambient conditions (see **Example 12**).

**Example 11.** Competitive slurry experiments

To determine the most thermodynamically favored crystalline of Compound A, competitive slurry experiments were carried out between Form 1 and Form 1\* by slurrying 1:1  
15 blends of both forms at 50°C and 5°C for 4 days then again after 10 days.

**Table 15.** Results from competitive slurry experiments

| Solvent system*        | Temp/°C | XRPD result |          |
|------------------------|---------|-------------|----------|
|                        |         | 4 d         | 10 d     |
| 2-Propanol             | 50      | 1           | N/A      |
| 2-Propanol:water 98:2  |         | 1           | N/A      |
| 2-Propanol:water 90:10 |         | 1           | N/A      |
| 2-Propanol:water 80:20 |         | 1           | N/A      |
| 2-Propanol:water 50:50 |         | 1           | N/A      |
| 2-Propanol:water 20:80 |         | Trace 1*    | 1        |
| Water                  |         | 1           | N/A      |
| 2-Propanol             | 20      | 1/1*        | 1 (PC)   |
| 2-Propanol:water 98:2  |         | 1/1*        | 1 (PC)   |
| 2-Propanol:water 90:10 |         | 1/1*        | IS       |
| 2-Propanol:water 80:20 |         | 1           | N/A      |
| 2-Propanol:water 50:50 |         | 1           | N/A      |
| 2-Propanol:water 20:80 |         | 1/1*        | Trace 1* |
| Water                  |         | PC          | Trace 1* |

\*numerical values are % by volume; PC = poorly crystalline;  
IS = insufficient solids; N/A = not applicable

*Results:*

As shown in Table 15, the solids recovered from the 2-propanol:water 20:80 % v/v experiment at 50 °C was mostly consistent with Form 1 but had traces of Form 1\*. The other 50 °C experiments were all consistent with Form 1. The solids recovered from the 2-propanol, 2-propanol:water 98:2 % v/v, 2-propanol:water 90:10 % v/v, and 2-propanol:water 20:80 % v/v experiments at 20 °C were mixtures of Form 1 and Form 1\*. The solids recovered from the 2-propanol:water 80:20 % v/v and 2-propanol:water 50:50 % v/v experiments at 20 °C were fully consistent with Form 1. The solids recovered from the water experiment at 20 °C were poorly crystalline.

Samples where Form 1\* peaks were observed, were re-slurried for an additional 6 days and then reanalyzed by XRPD at day 10. The results of this analysis indicated the solids recovered from the 2-propanol:water 20:80 % v/v experiment at 50 °C were fully converted to Form 1 (FIG. 25). The solids recovered from the 2-propanol and 2-propanol water 98:2 % v/v experiments at 20 °C were poorly crystalline but were otherwise consistent with conversion to Form 1. The solids recovered from the 2-propanol:water 20:80 % v/v and water experiments at 20 °C were predominantly consistent with Form with traces of Form 1\* (FIG. 26). Insufficient solids were recovered from the 2-propanol:water 90:10 % v/v experiment at 20 °C for further analysis. The foregoing results demonstrate that Form 1 is more stable than Form 1

**Example 12.** Characterization and stability studies of Form 1

During the course of crystallization studies, it was discovered that extensive drying of Form 1 solids under vacuum resulted in conversion to an additional polymorphic form, assigned as Form 4 (FIG. 8), with a decreased crystallinity upon further drying. It was subsequently found that Form 4 reverts back to Form 1 upon exposure to ambient atmospheric conditions.

To further investigate this interconversion, three experiments were carried out:

Experiment A: A 100 mg sample of the isolated dried solids from Form 1 were stored under ambient conditions in a sealed vial for 18 h.

Experiment B: A 100 mg sample of the isolated dried solids from Form 1 were stored under 25 °C/60 % RH conditions in an open vial for 18 h.

Experiment C: The bulk dried solids from Form 1 were stored under ambient conditions in an open vial for 18 h.

The solids from three above experiments were then analyzed by XRPD, TG/DSC, DSC, DVS, PLM, FT-IR, and KF.

Results:

5 The XRPD results (FIG. 27) indicated that the solids in Experiments A, B, and C reverted to Form 1 (with improved crystallinity) under all storage conditions assessed (including the bulk solids). The TG/DSC thermogram of Form 1 solids (FIG. 28) showed a 2.3 % loss from about 80-100°C. DSC analysis indicated three endothermic events during the first heating cycle (FIG. 29), the first with an onset temperature of 105 °C and a peak of 129 °C, the second had an onset temperature of 158 °C and a peak of 162 °C, and the third had an onset temperature of 174 °C and  
10 a peak of 177 °C. An exothermic event was observed during the cooling cycle (FIG. 30) with an onset temperature of 151 °C and a peak temperature of 147 °C. During the second heating cycle (FIG. 31), a glass transition was observed with a midpoint of 61 °C. An endothermic event was also observed, with an onset temperature of 182 °C and a peak of 196 °C. Polarized Light Microscopy (PLM) analysis of the bulk solids indicated the particles to be birefringent with  
15 needle/rod-like morphology consistent with Form 1 (FIG. 9). Dynamic vapor sorption (DVS) analysis indicated that the re-equilibrated Form 1 solids were slightly hygroscopic, a mass increase of 0.23 % was observed at 80 % RH (FIG. 32). A maximum hysteresis of 0.04 % was also observed. No form changes were observed post-DVS by XRPD. FT-IR analysis was carried out to provide baseline data for Form 1 (FIG. 10). Karl Fischer titration indicated a water content of  
20 2.2%, consistent with the 2.3 % mass loss observed at 90 °C in the TG/DSC analysis, indicating hemi-hydrate Form 1.

**Example 13. Bead Milling Assessment**

25 XRPD analysis of milled Form 1 material indicated a decline in crystallinity after 90 seconds of milling but no change in form. Further milling for >90 seconds had little effect on the form and crystallinity (FIG. 33).

**Example 14. TGA/DSC analysis of Form 3.**

30 Form 3 material isolated from the isopropyl acetate:heptane:acetonitrile:water 68:30:1:1 % primary polymorph screen evaporation experiment (**Example 5**, Procedure A) was also examined by TGA/DSC. The results (FIG. 34) indicated a gradual weight loss of 2.4% from the outset to



about 155 °C, followed by a steeper weight loss of 4.5% between 155 °C – 195 °C. Two endothermic events were observed at peak onsets 162 °C (peak at 173 °C) and 274 °C (at 283 °C). Based on these results, Form 3 appears to be a potential anhydrous form, but was observed to have relatively poor crystallinity by XRPD (FIG. 7).

5

Form 1

The Form 1 appears as birefringent fine needles/rods (see FIG. 9 for PLM images) with an X-ray powder diffraction (XRPD, see FIG. 4) pattern characterized by peaks at  $6.4 \pm 0.2$  degrees  $2\theta$ ,  $15.8 \pm 0.2$  degrees  $2\theta$ ,  $18.3 \pm 0.2$  degrees  $2\theta$ ,  $20.8 \pm 0.2$  degrees  $2\theta$ , and  $22.3 \pm 0.2$  degrees  $2\theta$ . See Table 16 for a list of XRPD peaks. The TG/DSC thermogram (FIG. 28) is characterized by a 2.3 % weight loss between 80-100 °C. The DSC first heat cycle thermogram (FIG. 29) is characterized three endothermic events, the first with an onset temperature of about 105 °C and a peak of about 129 °C, the second had an onset temperature of about 158 °C and a peak of about 162 °C and the third had an onset temperature of about 174 °C and a peak of about 177 °C. The first cooling DSC thermogram, shown in FIG. 30, is characterized by a single exothermic event at with an onset temperature of 151 °C and a peak temperature of 147 °C. Dynamic vapor sorption (DVS) analysis shows Form 1 as slightly hygroscopic, with a mass increase of 0.23 % at 80 % RH (FIG. 32), with a maximum hysteresis of 0.04 %. Karl Fischer titration shows Form 1 has a water content of 2.2%, consistent with the 2.3 % mass loss observed at 90 °C in the TG/DSC analysis, further indicating hemi-hydrate Form 1. Form 1 is obtained through crystallization of Compound A from MeOH/water or EtOH/water as described in Example 8 and MeOH/water as described in Example 9.

**Table 16.** XRPD peak list of Compound A, hemi-hydrate Form 1

| Peak No. | Pos. [ $2\theta$ ] | Rel. Int. [%] |
|----------|--------------------|---------------|
| 1        | 6.382              | 100           |
| 2        | 12.754             | 0.9           |
| 3        | 14.570             | 15.8          |
| 4        | 14.830             | 5.4           |
| 5        | 15.837             | 88.5          |
| 6        | 17.322             | 1.1           |
| 7        | 18.289             | 22.5          |
| 8        | 19.323             | 20.0          |
| 9        | 19.848             | 11.9          |

|    |        |      |
|----|--------|------|
| 10 | 20.525 | 7.8  |
| 11 | 20.842 | 22.3 |
| 12 | 21.257 | 5.1  |
| 13 | 21.511 | 12.8 |
| 14 | 21.780 | 7.1  |
| 15 | 22.327 | 22.5 |
| 16 | 22.786 | 14.3 |
| 17 | 23.138 | 2.8  |
| 18 | 24.026 | 17.4 |
| 19 | 25.077 | 6.7  |
| 20 | 25.343 | 12.9 |
| 21 | 25.833 | 5.5  |
| 22 | 26.130 | 2.7  |
| 23 | 26.863 | 16.8 |
| 24 | 27.230 | 4.7  |
| 25 | 27.609 | 11.0 |
| 26 | 27.952 | 13.2 |
| 27 | 28.271 | 15.4 |
| 28 | 28.659 | 4.3  |
| 29 | 29.201 | 15.3 |
| 30 | 29.606 | 6.4  |
| 31 | 30.333 | 3.4  |
| 32 | 30.729 | 2.1  |
| 33 | 31.269 | 15.5 |
| 34 | 31.873 | 4.8  |
| 35 | 32.330 | 2.0  |
| 36 | 32.808 | 1.2  |
| 37 | 33.374 | 4.5  |
| 38 | 33.806 | 1.5  |
| 39 | 34.173 | 2.2  |
| 40 | 34.667 | 1.0  |
| 41 | 35.377 | 2.4  |
| 42 | 36.011 | 1.2  |
| 43 | 37.363 | 1.0  |
| 44 | 38.040 | 2.7  |
| 45 | 38.403 | 1.1  |
| 46 | 39.107 | 1.3  |
| 47 | 39.568 | 0.9  |

Additional properties of Form 1 are shown in Table 17 below:

Table 17. General Properties of Compound A, hemi-hydrate Form 1.

| Property       | Description       |
|----------------|-------------------|
| Physical state | Crystalline solid |

| Property                         | Description                                                                                                                                                         |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Optical activity                 | Single enantiomer, ( <i>R</i> )-configuration                                                                                                                       |
| Melting range                    | 178.6 °C onset; 180.5 °C sharp peak (endotherms at 123 °C and 166 °C (dehydration and possible form change)                                                         |
| Hygroscopicity                   | Non-hygroscopic                                                                                                                                                     |
| Organic solubility (mg/mL)       | 4:1 acetonitrile-water >1<br>Methanol 200<br>Ethanol 90<br>Isopropanol 70<br>Acetone 130<br>MTBE 9<br>Heptane <10<br>Dichloromethane <10<br>Dimethyl acetamide >500 |
| Aqueous solubility (µg/mL)       | 0.1N HCl (pH 2) 29<br>25mM NaOAc (pH 4) 7<br>PBS/Blank FaSSIF (pH 6.5) 5<br>Water 8                                                                                 |
| pKa                              | 2.6                                                                                                                                                                 |
| Log P                            | 3.5                                                                                                                                                                 |
| Log D <sub>7.4</sub>             | 3.6                                                                                                                                                                 |
| Permeability, Papp (A-B), Caco-2 | 13 (10 <sup>-6</sup> cm/s)                                                                                                                                          |

Form 1\*

The Form 1\* appears as birefringent fine needles (see FIG. 1 for PLM images) with an X-ray powder diffraction (XRPD, see FIG 2) pattern characterized by peaks at  $6.3 \pm 0.2$  degrees  $2\theta$ ,  $15.8 \pm 0.2$  degrees  $2\theta$ ,  $20.8 \pm 0.2$  degrees  $2\theta$ ; while the XRPD pattern is similar to Form 1, Form 1\* appears to lack the pronounced peak at  $18.3 \pm 0.2$  degrees  $2\theta$  present in Form 1 as well as other peaks present in Form 1 as indicated in FIG. 2, e.g., at  $22.8 \pm 0.2$  degrees  $2\theta$  and  $25.3 \pm 0.2$  degrees  $2\theta$ . See Table 18 for a list of XRPD peaks. The Thermal Gravimetric/Differential Scanning Calorimetry (TG/DSC) thermogram of Form 1\* (FIG. 3) is characterized by multiple weight loss events prior to degradation, with a 2.5 % weight loss between 72 °C and 114 °C (theoretically equivalent to 0.5 moles of water), 2.2 % weight loss between 147 °C and 185 °C (theoretically equivalent to 0.5 moles of water) and a 12.2 % weight loss between 185 °C and 252 °C; the TG/DSC thermogram shows an endothermic event at peak onset 86 °C (peak at 102 °C) associated with the first weight loss, followed by overlapping endothermic events, the first with onset 154 °C (peak at 158 °C) and the second with onset 172 °C (peak at 176 °C), associated with the second

weight loss. An endothermic event associated with degradation was observed with an onset of 294 °C (peak 301 °C). Form 1 is obtained through crystallization of Compound A from Acetone/water (70:30), Acetonitrile/water (95:5) as described in Example 5.

5 **Table 18.** XRPD peak list of Compound A Form 1\*

| Peak No. | Pos. [°2θ] | Rel. Int. [%] |
|----------|------------|---------------|
| 1        | 3.1615     | 6.26          |
| 2        | 6.2909     | 100           |
| 3        | 9.0544     | 0.04          |
| 4        | 14.429     | 12.41         |
| 5        | 14.4887    | 12.31         |
| 6        | 14.7308    | 4.96          |
| 7        | 15.7745    | 39.57         |
| 8        | 15.9267    | 29.21         |
| 9        | 17.0463    | 4.53          |
| 10       | 17.4792    | 3.79          |
| 11       | 18.2071    | 2.92          |
| 12       | 18.944     | 8.48          |
| 13       | 19.3126    | 21.63         |
| 14       | 19.7774    | 27.24         |
| 15       | 20.324     | 9.36          |
| 16       | 20.8264    | 38.52         |
| 17       | 21.5588    | 12.75         |
| 18       | 22.1463    | 18.54         |
| 19       | 22.8411    | 3.74          |
| 20       | 23.5712    | 6.66          |
| 21       | 23.9696    | 18.78         |
| 22       | 24.5263    | 5.67          |
| 23       | 25.0616    | 3.53          |
| 24       | 26.0886    | 11.18         |
| 25       | 26.4312    | 12.98         |
| 26       | 26.7912    | 9.02          |
| 27       | 27.5589    | 18.96         |
| 28       | 27.9409    | 20.38         |
| 29       | 28.6091    | 9.83          |
| 30       | 29.1798    | 14.61         |
| 31       | 29.6466    | 5.9           |
| 32       | 31.1945    | 9.09          |
| 33       | 31.4998    | 8.17          |
| 34       | 33.4176    | 2.18          |
| 35       | 34.4498    | 0.76          |

Form 2

The Form 2 has an X-ray powder diffraction (XRPD, see FIG 6) pattern characterized by peaks at  $6.2 \pm 0.2$  degrees  $2\theta$ ,  $15.2 \pm 0.2$  degrees  $2\theta$ ,  $20.9 \pm 0.2$  degrees  $2\theta$ , and  $21.9 \pm 0.2$  degrees  $2\theta$ . See Table 19 for a list of XRPD peaks.

5

Table 19. XRPD peak list of Compound A Form 2

| Peak No. | Pos. [ $^{\circ}2\theta$ ] | Rel. Int. [%] |
|----------|----------------------------|---------------|
| 1        | 6.227                      | 100           |
| 2        | 9.3397                     | 3.55          |
| 3        | 12.4542                    | 0.84          |
| 4        | 13.9444                    | 6.0           |
| 5        | 14.261                     | 10.65         |
| 6        | 14.6778                    | 29.37         |
| 7        | 15.2248                    | 69.14         |
| 8        | 15.2597                    | 66.84         |
| 9        | 15.6062                    | 11.48         |
| 10       | 16.7543                    | 4.68          |
| 11       | 17.6937                    | 22.18         |
| 12       | 18.6702                    | 42.23         |
| 13       | 18.7251                    | 45.89         |
| 14       | 19.4439                    | 26.79         |
| 15       | 19.9397                    | 27.38         |
| 16       | 20.5801                    | 29.01         |
| 17       | 20.9061                    | 64.12         |
| 18       | 20.9922                    | 58.27         |
| 19       | 21.0903                    | 37.62         |
| 20       | 21.5049                    | 23.07         |
| 21       | 21.902                     | 59.68         |
| 22       | 21.9567                    | 58.55         |
| 23       | 22.5669                    | 10.39         |
| 24       | 23.3                       | 5.36          |
| 25       | 23.9946                    | 38.81         |
| 26       | 25.0141                    | 12.31         |
| 27       | 26.046                     | 22.06         |
| 28       | 26.9273                    | 40.28         |
| 29       | 27.3673                    | 35.24         |
| 30       | 27.6569                    | 16.67         |
| 31       | 28.0214                    | 30.61         |
| 32       | 28.2929                    | 18.68         |
| 33       | 29.0846                    | 8.1           |
| 34       | 29.4458                    | 7.33          |
| 35       | 30.4876                    | 17.78         |

|    |         |       |
|----|---------|-------|
| 36 | 30.7942 | 15.99 |
| 37 | 31.447  | 10.44 |
| 38 | 31.675  | 9.89  |
| 39 | 33.1576 | 4.93  |
| 40 | 33.9676 | 2.22  |
| 41 | 34.289  | 5.89  |

Form 3

The crystalline Form 3 is poorly crystalline, (see XRPD in FIG. 7), with an X-ray powder diffraction pattern characterized by a major peak at  $4.0 \pm 0.2$  degrees  $2\theta$ , and several relatively smaller peaks at  $4.9 \pm 0.2$  degrees  $2\theta$ ,  $9.1 \pm 0.2$  degrees  $2\theta$ , and  $21.4 \pm 0.2$  degrees  $2\theta$ . See Table 20 for a list of XRPD peaks. The TG/DSC thermogram (FIG. 34) is characterized by a gradual weight loss of 2.4 % from the outset to about 155 °C, followed by a steeper weight loss of 4.5% between 155 °C – 195 °C. The DSC thermogram of Form 3 (FIG. 34) is characterized by two endothermic events, one with an onset of about 162 °C and peak of about 173 °C, and one with a peak onset of about 274 °C peak of about 283 °C. Form 3 is obtained through crystallization of Compound A from butyl acetate, ethyl acetate, methylisobutyl ketone, or tetrahydrofuran as described in Example 5.

Table 20. XRPD peak list of Compound A Form 3

| Peak No. | Pos. [ $^{\circ}2\theta$ ] | Rel. Int. [%] |
|----------|----------------------------|---------------|
| 1        | 3.9589                     | 100           |
| 2        | 4.9415                     | 18.58         |
| 3        | 6.2186                     | 6.5           |
| 4        | 6.8758                     | 9.76          |
| 5        | 7.5069                     | 5.01          |
| 6        | 9.059                      | 12.73         |
| 7        | 9.891                      | 8.92          |
| 8        | 14.3074                    | 8.54          |
| 9        | 15.6833                    | 9.5           |
| 10       | 16.8419                    | 9.42          |
| 11       | 19.2236                    | 11.45         |
| 12       | 21.431                     | 12.99         |
| 13       | 23.8848                    | 7.86          |
| 14       | 25.8435                    | 13.39         |
| 15       | 31.7004                    | 2.17          |

Form 4

The Form 4 is has an X-ray powder diffraction (XRPD, see FIG. 8) pattern characterized by peaks at  $6.3 \pm 0.2$  degrees  $2\theta$ ,  $15.5 \pm 0.2$  degrees  $2\theta$ , and  $20.9 \pm 0.2$  degrees  $2\theta$ . See Table 21 for a list of XRPD peaks. Form 4 is obtained through over drying Form 1, and will rapidly revert back to Form 1 when allowed to equilibrate under ambient conditions as shown in Example 12.

5

**Table 21.** XRPD peak list of Compound A Form 4

| Peak No. | Pos. [ $^{\circ}2\theta$ ] | Rel. Int. [%] |
|----------|----------------------------|---------------|
| 1        | 3.1301                     | 16.83         |
| 2        | 6.2768                     | 100           |
| 3        | 14.3853                    | 7.91          |
| 4        | 14.9231                    | 23.27         |
| 5        | 15.4959                    | 41.17         |
| 6        | 15.7553                    | 25.39         |
| 7        | 16.1805                    | 3.96          |
| 8        | 17.9319                    | 11.32         |
| 9        | 18.0915                    | 10.92         |
| 10       | 18.9868                    | 12.05         |
| 11       | 19.3022                    | 19.11         |
| 12       | 19.8694                    | 19.31         |
| 13       | 20.4702                    | 21.43         |
| 14       | 20.9398                    | 48.42         |
| 15       | 21.5143                    | 30.23         |
| 16       | 22.1319                    | 15.33         |
| 17       | 22.5071                    | 10.38         |
| 18       | 22.6327                    | 10.14         |
| 19       | 23.0762                    | 2.47          |
| 20       | 24.0728                    | 34.73         |
| 21       | 25.0112                    | 14.44         |
| 22       | 25.8407                    | 8.1           |
| 23       | 26.8649                    | 20.4          |
| 24       | 27.2831                    | 15.41         |
| 25       | 27.6715                    | 28.72         |
| 26       | 28.1271                    | 18.15         |
| 27       | 28.4021                    | 17.23         |
| 28       | 29.0527                    | 13.42         |
| 29       | 29.564                     | 7.14          |
| 30       | 30.2499                    | 4.93          |
| 31       | 30.8465                    | 12.95         |
| 32       | 33.4255                    | 3.56          |
| 33       | 34.442                     | 2.57          |

Compound A mesylate salt

The crystalline form of Compound A mesylate salt has a TG/DSC thermogram (FIG. 14) characterized by one endothermic event with an onset temperature of 200 °C and a peak temperature of 207 °C. The crystalline mesylate salt has an X-ray powder diffraction (XRPD) that substantially appears as the diffractogram shown in FIG 13. The crystalline mesylate salt rapidly dissociates back to (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea freebase in pH 1.2, pH 4.5 and 6.8 buffers as shown in Example 2 and FIG. 15. (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea mesylate salt in obtained by treating Compound A with 1.05 molar equivalents of methane-sulfonic acid solution followed by crystallization from ethyl acetate as described in Example 2.

Example 15. Formulation of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea

Tablets including Form 1 as the active pharmaceutical ingredient (API) were manufactured using the excipients shown in Table 22. Opadry II film coat is accepted on CoA and supplier specification. Table 23, Table 24 and Table 25 include film coat specifications. Table 26 shows the amount of each component in 5 mg and 20 mg tablets.

Table 22. Excipients, Manufacturers and Compendial Grade for Tablet.

| Excipient                                        | (Manufacturer)                                               | Compendial Grade                                                   |
|--------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------|
| Microcrystalline Cellulose                       | Avicel PH101 (Dupont)                                        | NF <sup>1</sup> , Ph. Eur. <sup>2</sup> , JP <sup>3</sup>          |
| Mannitol                                         | Parteck M100 (Millipore)                                     | Ph. Eur, BP <sup>4</sup> , ChP <sup>5</sup> , JP, USP <sup>6</sup> |
| Croscarmellose Sodium                            | Ac-Di-Sol SD 711 (Dupont)                                    | NF, Ph. Eur., JP                                                   |
| Colloidal Silicon Dioxide, 200 m <sup>2</sup> /g | Colloidal, highly dispersed<br>Emprove Essential (Millipore) | Ph. Eur., NF, JP                                                   |
| Sodium Stearyl Fumarate                          | PRUV (JRS Pharma)                                            | Ph. Eur., NF, JPE <sup>7</sup>                                     |

<sup>1</sup>National Formulary. <sup>2</sup>European Pharmacopoeia. <sup>3</sup>Japanese Pharmacopoeia. <sup>4</sup>British Pharmacopoeia. <sup>5</sup>Chinese Pharmacopoeia. <sup>6</sup>US Pharmacopoeia. <sup>7</sup>Japanese Pharmaceutical Excipients.

Table 23. Film Coat, Manufacturer and Quality standard for Tablet.

| Excipient                          | Trade name (Manufacturer) | Acceptance Criteria |
|------------------------------------|---------------------------|---------------------|
| Film coat, White (P/N: 85F18422)   | Opadry II (Colorcon)      | CoA, Specification  |
| Film coat, Yellow (P/N: 85F120220) | Opadry II (Colorcon)      | CoA, Specification  |

Table 24. Opadry II Film Coat, White (85F18422) Specification (Colorcon).

| Test                     | Acceptance Criteria   |
|--------------------------|-----------------------|
| Color difference DE, CIE | 0–1.5 or visual match |
| Color difference, visual | Compares              |



|                 |              |
|-----------------|--------------|
| Ash content (%) | 35.80–43.80  |
| Appearance      | White powder |
| Dispersion      | Pass         |
| Speck check     | Pass         |
| IR scan         | Compares     |

Table 25. Opadry II Film Coat, Yellow (85F120220) Specification (Colorcon).

| Test                     | Method             | Acceptance Criteria              |
|--------------------------|--------------------|----------------------------------|
| Color difference DE, CIE | GLO-QC-TM-0576/D28 | 0–3.0 or visual match            |
| Color difference, visual | GLO-QC-TM-0576     | Compares                         |
| Ash content (%)          | GLO-QC-TM-0699     | 35.31–43.31                      |
| Product Appearance       | GLO-QC-TM-0733     | Conforms to material description |
| Dispersion               | GLO-QC-TM-0729     | Pass                             |
| Speck check              | GLO-QC-TM-0730     | Pass                             |
| IR scan                  | GLO-QC-TM-0744     | Compares                         |

Table 26. Composition of 5 mg and 20 mg Tablets.

| Component                                       | Function       | Grade             | Theoretical Amount (%) | 5 mg Tablet | 20 mg Tablet |
|-------------------------------------------------|----------------|-------------------|------------------------|-------------|--------------|
| <i>Intragranular</i>                            |                |                   |                        |             |              |
| Form 1                                          | API            | Specification     | 5.0                    | 5.0         | 20.0         |
| Microcrystalline Cellulose                      | Ductile filler | NF, Ph. Eur., JP  | 44.6                   | 44.6        | 178.5        |
| Mannitol                                        | Brittle filler | Ph. Eur., USP     | 44.9                   | 44.9        | 179.5        |
| Croscarmellose sodium                           | Disintegrant   | NF, Ph. Eur.      | 2.0                    | 2.0         | 8.0          |
| Colloidal silicon dioxide 200 m <sup>2</sup> /g | Flow aid       | NF                | 0.75                   | 0.75        | 3.0          |
| Sodium stearyl fumarate                         | Lubricant      | Ph. Eur., NF, JPE | 0.75                   | 0.75        | 3.0          |
|                                                 |                |                   | 98.0                   | 98.0        | 392.0        |
| <i>Extragranular</i>                            |                |                   |                        |             |              |
| Croscarmellose sodium                           | Disintegrant   | NF, Ph. Eur.      | 1.0                    | 1.0         | 4.0          |
| Colloidal silicon dioxide 200 m <sup>2</sup> /g | Flow aid       | NF                | 0.50                   | 0.50        | 2.0          |
| Sodium stearyl fumarate                         | Lubricant      | Ph. Eur., NF, JPE | 0.50                   | 0.50        | 2.0          |
| Core total                                      |                |                   | 100.0                  | 100.0       | 400.0        |
| <i>Coating</i>                                  |                |                   |                        |             |              |
| Opadry II                                       | Cosmetic coat  |                   | 3.0                    | 3.0         | 12.0         |
| Coated tablet total (mg)                        |                |                   | N/A                    | 103.0       | 412.0        |

**WHAT IS CLAIMED IS:**

1. A crystalline form of (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof.

2. The crystalline form of claim 1, wherein the (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea is present in the form of a pharmaceutically acceptable solvate.

3. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 1 characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $18.3 \pm 0.2$  degrees  $2\theta$ .

4. The crystalline form of claim 3, wherein the XRPD pattern has a peak at  $15.8 \pm 0.2$  degrees  $2\theta$ .

5. The crystalline form of any one of claims 3-4, wherein the XRPD pattern has a peak at  $6.4 \pm 0.2$  degrees  $2\theta$ .

6. The crystalline form of any one of claims 3-5, wherein the XRPD pattern has a peak at  $22.3 \pm 0.2$  degrees  $2\theta$ .

7. The crystalline form of any one of claims 3-6, wherein the XRPD pattern has a peak at  $20.8 \pm 0.2$  degrees  $2\theta$ .

8. The crystalline form of any one of claims 3-7, wherein the XRPD pattern has a peak at  $19.3 \pm 0.2$  degrees  $2\theta$ .

9. The crystalline form of any one of claims 3-8, wherein the XRPD pattern has a peak at  $24.0 \pm 0.2$  degrees  $2\theta$ .

10. The crystalline form of any one of claims 3-9, wherein the XRPD pattern has a peak at  $26.9 \pm 0.2$  degrees  $2\theta$ .

5 11. The crystalline form of any one of claims 3-10, wherein the XRPD pattern has a peak at  $14.6 \pm 0.2$  degrees  $2\theta$ .

12. The crystalline form of any one of claims 3-11, wherein the XRPD pattern has a peak at  $31.3 \pm 0.2$  degrees  $2\theta$ .

10

13. The crystalline form of any one of claims 3-12, wherein the XRPD pattern has a peak at  $28.3 \pm 0.2$  degrees  $2\theta$ .

14. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 1, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 15.8, and 18.3.

15

15. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 1, and wherein the XRPD pattern has peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.4, 14.6, 15.8, 18.3, 19.3, 20.8, 22.3, 24.0, 26.9, 28.3, 29.2 and 31.3.

20

16. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 1, characterized by an XRPD pattern substantially the same as that shown in FIG. 4.

17. The crystalline form of any one of claims 1-16, wherein the crystalline form is Form 1 having a thermogravimetric analysis (TGA) curve characterized by a weight loss of about 2.3% at about 112.5 °C.

25

18. The crystalline form of any one of claims 1-17, wherein the crystalline form is Form 1 having a TGA curve characterized by a weight loss of about 17.6% at about 245 °C.

30

19. The crystalline form of any one of claims 1-18, wherein the crystalline form is Form 1 having a TGA curve that is substantially the same as that shown in FIG. 28.

20. The crystalline form of any one of claims 1-19, wherein the crystalline form is Form 1 prepared by a method comprising:

- (a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in isopropanol to form a solution;
- (b) adding water to the solution to form a mixture;
- (c) reducing the temperature of the mixture then maintaining the temperature for a first period of time;
- (d) increasing the temperature of the mixture then maintaining the temperature for a second period of time;
- (e) reducing the temperature of the mixture then maintaining the temperature for a third period of time; and
- (f) isolating Form 1 from the mixture.

21. The crystalline form of any one of claims 1-4, wherein the crystalline form is Form 1 prepared by a method comprising:

- (a) dissolving (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea, or a pharmaceutically acceptable salt and/or solvate thereof in methanol to form a solution;
- (b) adding water to the solution to form a first mixture;
- (c) adding (R)-1-(2-aminopyrimidin-5-yl)-3-(1-(5,7-difluoro-3-methylbenzofuran-2-yl)-2,2,2-trifluoroethyl)urea Form 1 to the first mixture to form a second mixture;
- (d) agitating the second mixture;
- (e) adding water to the second mixture to form a third mixture;
- (f) agitating the third mixture; and
- (g) isolating Form 1 from the third mixture.

22. The crystalline form of claim 21, wherein isolating Form 1 from the third mixture comprises:

- (i) filtering the third mixture to provide a solid;
- (ii) rinsing the solid with methanol and water; and
- (iii) drying the solid to provide Form 1.

23. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 1\* characterized by an X-ray powder diffraction (XRPD) pattern having a peak at  $6.3 \pm 0.2$  degrees  $2\theta$ .

24. The crystalline form of claim 23, wherein the XRPD pattern has a peak at  $15.8 \pm 0.2$  degrees  $2\theta$ .

25. The crystalline form of any one of claims 23-24, wherein the XRPD pattern has a peak at  $20.8 \pm 0.2$  degrees  $2\theta$ .

26. The crystalline form of any one of claims 23-25, wherein the XRPD pattern has a peak at  $15.9 \pm 0.2$  degrees  $2\theta$ .

27. The crystalline form of any one of claims 23-26, wherein the XRPD pattern has a peak at  $19.8 \pm 0.2$  degrees  $2\theta$ .

28. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 2 characterized by an X-ray powder diffraction (XRPD) pattern having peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.2, 15.2, 15.3, 20.9, 21.9, 22.0, 21.0, 18.7, 18.7, and 26.9.

29. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 3 characterized by an X-ray powder diffraction (XRPD) pattern having peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 4.0, 4.9, 25.8, 21.4, 9.1, 19.2, 6.9, 15.7, 16.8, and 9.9.

30. The crystalline form of any one of claims 1-2, wherein the crystalline form is Form 4 characterized by an X-ray powder diffraction (XRPD) pattern having peaks ( $\pm 0.2$  degrees  $2\theta$ ) at 6.3, 20.9, 15.5, 24.1, 21.5, 27.7, 15.8, 14.9, 20.5, and 26.9.

5 31. A pharmaceutical composition comprising the crystalline form of any one of claims 1-30 and a pharmaceutically acceptable carrier.

32. The pharmaceutical composition of claim 31, wherein the composition is in the form of a tablet.

10 33. The pharmaceutical composition of any one of claims 31-32, wherein the composition comprises microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate, or any combination thereof.

15 34. A method for treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the crystalline form of any one of claims 1-30, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition of any one of claims 31-33.

20 35. A method for treating cancer in a subject in need thereof, the method comprising (a) determining that the cancer is associated with a dysregulation of a *PIK3CA* gene, a PI3K $\alpha$  protein, or expression or activity or level of any of the same; and (b) administering to the subject a therapeutically effective amount of the crystalline form of any one of claims 1-30, or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition of any  
25 one of claims 31-33.

30 36. A method of treating a PI3K $\alpha$ -associated cancer in a subject, the method comprising administering to a subject identified or diagnosed as having a PI3K $\alpha$ -associated cancer a therapeutically effective amount of the crystalline form of any one of claims 1-30 or a pharmaceutically acceptable salt and/or solvate thereof, or a pharmaceutical composition of any one of claims 31-33.

37. A method for modulating PI3K $\alpha$  in a mammalian cell, the method comprising contacting the mammalian cell with an effective amount of the crystalline form of any one of claims 1-30, or a pharmaceutically acceptable salt and/or solvate thereof.