

250 mg of CYT-0387 free base. In certain embodiments, the application is directed to dosage forms comprising CYT-0387 dihydrochloride monohydrate Form II, as a tablet, wherein the dosage forms comprising comprises CYT-0387 dihydrochloride monohydrate Form II in an amount equivalent to about 300 mg of CYT-0387 free base. In additional embodiments, the application is directed to dosage forms or pharmaceutical compositions comprising CYT-0387 dihydrochloride monohydrate Form II in an amount equivalent to 200 mg of CYT-0387 free base which provide a pharmacokinetic profile substantially similar to a dosage form or pharmaceutical composition comprising the CYT-0387 dihydrochloride monohydrate Form II in an amount equivalent to 300 mg of CYT-0387 free base.

Also provided is a kit that includes a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof. The kit may further comprise a label and/or instructions for use of the compound in treating a disease, disorder, or condition in a human in need thereof.

Also provided are articles of manufacture that include a compound of formula (I) or a pharmaceutically acceptable salt, isomer, or a mixture thereof, and a container. In one embodiment, the container may be a vial, jar, ampoule, preloaded syringe, or an intravenous bag.

DESCRIPTION OF THE FIGURES

Figure 1: XRPD of N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT-0387) dihydrochloride anhydrous Form I.

Figure 2: DSC of N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT-0387) dihydrochloride anhydrous Form I.

Figure 3: TGA of N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT-0387) dihydrochloride anhydrous Form I.

Figure 4: DVS of N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT-0387) dihydrochloride anhydrous Form I.

Figure 5: XRPD pattern for N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II.

Figure 6, DSC in Figure 9, or TGA in Figure 12. In one embodiment, Form I or CYT-0387 Form I has an XRPD pattern having peaks at about 13.5°, 20.9°, 26.1°, 26.6°, and 28.3° $2\theta \pm 0.2^\circ 2\theta$.

In some embodiment, Form II or CYT-0387 Form II is characterized by XRPD shown in Figure 5, DSC in Figure 8, TGA in Figure 11, or DVS in Figure 14. In one embodiment, Form II or CYT-0387 Form II has an XRPD pattern having peaks at about 7.7°, 19.3°, 24.0°, 25.7°, and 29.6° $2\theta \pm 0.2^\circ 2\theta$.

In other embodiment, Form III or CYT-0387 Form III is characterized by XRPD shown in Figure 7, DSC in Figure 10, or TGA in Figure 13. In one embodiment, Form III or CYT-0387 Form III has an XRPD pattern having peaks at about 12.7°, 14.6°, 17.8°, 19.7°, and 23.3° $2\theta \pm 0.2^\circ 2\theta$.

In certain embodiment, Form IV or CYT-0387 Form IV is characterized by XRPD shown in Figure 1, DSC in Figure 2, or TGA in Figure 3. In one embodiment, Form IV or CYT-0387 Form IV has an XRPD pattern having peaks at about 5.5°, 10.1°, 14.9°, 25.1°, and 26.6° $2\theta \pm 0.2^\circ 2\theta$.

Results of the present application found that CYT-0387 dihydrochloride monohydrate (Form II) has the increased stability than other salts or forms of CYT-387 at certain conditions. The results described herein also found that such properties of CYT-387 Form II makes it more suitable for developing or adopting to various synthesis or process. In one embodiment, CYT-387 Form II is suitable for use in a pharmaceutical composition in the tablet format. Also, the studies described herein showed the tablet formulation exhibited bioavailability properties similar to those of capsule formulations. In certain embodiments, a tablet comprising CYT-0387 dihydrochloride monohydrate Form II in an amount equivalent to 200mg of free base of CYT-0387 provides similar bioavailability as a capsule comprising CYT-0387 dihydrochloride anhydrous Form I in an amount equivalent to 300mg of free base of CYT-0387.

The results of present application indicate that CYT-0387 dihydrochloride anhydrous Form I was hygroscopic and physically unstable when exposed to moisture. Also, the results described below indicate that CYT-0387 dihydrochloride monohydrate Form II is a

The XRPD pattern for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II is represented in Figure 5.

The XRPD pattern for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form I is represented in Figure 6.

5 The XRPD pattern for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form III is represented in Figure 7.

XRPD peaks of the various CYT-0387 forms are found in Table 1 above.

Differential scanning calorimetry: Thermal properties of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II were
10 evaluated using a Differential Scanning Calorimetry (DSC) instrument (TA Q1000, TA Instruments, New Castle, DE, USA). Approximately 5 to 10 mg of solid sample was placed in a standard aluminum pan vented with a pinhole for each experiment and heated at a rate of 10 °C/min under a 50 mL/min nitrogen purge. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA). Heat of fusion analysis
15 was conducted by sigmoidal integration of the endothermic melting peak.

The DSC for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II is represented in Figure 8.

The DSC for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form I is represented in Figure 9.

20 The DSC for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form III is represented in Figure 10.

Thermogravimetric analysis: Thermogravimetric analysis (TGA) of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II was performed on a TGA instrument (TA Q500, TA Instruments, New Castle, DE, USA).
25 Approximately 5 to 10 mg of solid sample was placed in an open aluminum pan for each experiment and heated at a rate of 10 °C/min under a 60 mL/min nitrogen purge using. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments, New Castle, DE, USA).

The TGA for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II is represented in Figure 11.

The TGA for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form I is represented in Figure 12.

5 The TGA for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form III is represented in Figure 13.

Dynamic vapor sorption: The hygroscopicity of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II was evaluated at room temperature using a dynamic vapor sorption (DVS) instrument (TGA Q5000
10 TA Instruments, New Castle, DE). Water adsorption and desorption were studied as a function of relative humidity (RH) over the range of 0 to 90% at room temperature. The humidity in the chamber was increased from the initial level 50% RH to 60% RH and held until the solid and atmosphere reached equilibration. The equilibrium test was continued until passed or expired after 10 hours. At this point, RH was raised 10% higher and the process was repeated until 90%
15 RH was reached and equilibrated. During this period, the water sorption was monitored. For desorption, the relative humidity was decreased in a similar manner to measure a full sorption/desorption cycle. All experiments were operated in dm/dt mode (mass variation over time) to determine the equilibration endpoint. Approximately 4 mg of solid CYT-0387 was used. Data analysis was conducted using Universal Analysis 2000 Version 4.7A (TA Instruments,
20 New Castle, DE, USA).

The DVS for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II is represented in Figure 14.

The single crystal X-ray crystallography data for *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT-0387) dihydrochloride monohydrate
25 Form II and *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide CYT-0387) monohydrochloride anhydrous Form I is summarized in Table 2 below. Data from further characterization of the crystals are summarized in Table 3 below.

What is Claimed:

1. A compound selected from the group consisting of:

N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II;

5 *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form I; and

N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form III.

2. The compound of claim 1 in a crystalline form.

10 3. The crystalline form of claims 1-2, wherein the crystalline form is *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II.

4. The crystalline form of claim 3, wherein the crystals have unit cell parameters at $T=100^{\circ}\text{K}$ of: $a = 10.2837(6) \text{ \AA}$, $b = 10.4981(6) \text{ \AA}$, $c = 11.5143(7) \text{ \AA}$, $\alpha = 83.297(2)^{\circ}$, $\beta = 87.649(2)^{\circ}$, $\gamma = 67.445(2)^{\circ}$, and a triclinic *P*-1 space group.

15 5. The crystalline form of claim 3, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 5.

6. The crystalline form of claim 3, characterized by an x-ray powder diffraction (XRPD) pattern having peaks at about 7.7° , 19.3° , 24.0° , 25.7° , and $29.6^{\circ} 2\theta \pm 0.2^{\circ} 2\theta$.

20 7. The crystalline form of claim 3, characterized by differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 8.

8. The crystalline form of claim 3, characterized by a dynamic vapor sorption (DVS) pattern substantially as set forth in Figure 14.

9. The crystalline form of claim 2, wherein the crystalline form is Crystalline *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form I.

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10. The crystalline form of claim 9, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 6.
11. The crystalline form of claim 9, characterized by an X-ray powder diffraction ("XRPD") pattern having peaks at about 13.5°, 20.9°, 26.1°, 26.6°, and 28.3° 2-θ ± 0.2 ° 2-θ.
- 5 12. The crystalline form of claim 9, characterized by a differential scanning calorimetry (DSC) pattern substantially as set forth in Figure 9.
13. The crystalline form of claim 2, wherein the crystalline form is crystalline *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide monohydrochloride anhydrous Form III.
- 10 14. The crystalline form of claim 13, characterized by an x-ray powder diffraction (XRPD) pattern substantially as set forth in Figure 7.
15. The crystalline form of claim 13, characterized by an X-ray powder diffraction ("PXRD") pattern having peaks at about 12.7°, 14.6°, 17.8°, 19.7°, and 23.3° 2-θ ± 0.2 ° 2-θ.
16. The crystalline form of claim 13, characterized by a differential scanning calorimetry
15 (DSC) pattern substantially as set forth in Figure 10.
17. A pharmaceutical composition comprising a compound of any of claims 1-16.
18. The pharmaceutical composition of claim 17, wherein the compound of claim 1 is *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II.
- 20 19. The pharmaceutical composition of claims 17-18 wherein *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride monohydrate Form II is present at an amount equivalent to 50 mg, 100 mg, 150 mg, or 200 mg of free base *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide.
20. The pharmaceutical composition of any one of claims 17-19 in the form of a tablet.

21. The pharmaceutical composition of any of claims 17-20, wherein after a single oral administration said composition provides:

a $C_{\max}$ in the range of 260 to 405 ng/mL of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide,

5 an $AUC_{\inf}$ in the range of 2,057 to 3,214 ng·hr/mL of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide, or

both a $C_{\max}$ in the range of 260 to 405 ng/mL of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide and an $AUC_{\inf}$ in the range of 2,057 to 3,214 ng·hr/mL of *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide.

10 22. The pharmaceutical composition of claim 21, wherein after a single oral administration said composition provides a pharmacokinetic profile substantially similar to that of a dosage form comprising *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide dihydrochloride anhydrous Form I in an amount equivalent to 300 mg of free base *N*-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide.