

CLAIMS

1. ~~Polymorph C of N~~ A method of preparing a solid crystalline form of a N-((4,6-
dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl-(tetrahydro-2H-pyran-4-yl)amino)-4-
methyl-4',4'-(morpholinomethyl)-[1,1',1'-biphenyl]-3-
5 ~~-carboxamide monohydrochloride.~~

2. ~~The polymorph according to claim 1, wherein the polymorph~~ solid crystalline form
exhibits an X-ray powder diffraction pattern having two or more ~~characteristic~~ peaks expressed
in degrees 2-theta (+/- 0.2) ~~at 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.~~

3. ~~The polymorph according to claim 1, wherein the polymorph exhibits an X-ray powder~~
~~diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta (+/-~~
~~0.2) at 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.~~

4. ~~The polymorph according to claim 1, wherein the polymorph exhibits an X-ray powder~~
~~diffraction pattern having four or more characteristic peaks expressed in degrees 2-theta (+/- 0.2)~~
~~at 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.~~

5. ~~The polymorph according to claim 1, wherein the polymorph exhibits an X-ray powder~~
20 ~~diffraction pattern having characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 17.53,~~
~~21.14, 23.46, and 27.72.~~

6. ~~The polymorph according to claim 1, wherein the polymorph exhibits an X-ray powder~~
~~diffraction pattern having at least eight characteristic peaks expressed in degrees 2-theta (+/- 0.2),~~
25 ~~selected from the group consisting of 8.438, 10.08083, 10.94, 16.58, 17.12, 17.53, 18.34, 18.66,~~
~~20.50, 21.14, 21.92, 22.22, 23.46, 26.22, 26.60, 27.72, and 30.30.~~

7. ~~The polymorph according to claim 1, wherein the polymorph exhibits an X-ray powder~~
~~diffraction pattern having at least nine characteristic peaks expressed in degrees 2-theta (+/- 0.2),~~
30 ~~selected from the group consisting of 10.0818, 10.94, 16.58, 17.12, 17.53, 18.34, 18.66, 20.50,~~
~~21.14, 21.92, 22.22, 23.46, 26.22, 26.60, 27.72, and 30.30.~~

8. — The polymorph according to claim 1, wherein the polymorph exhibits an X-ray powder diffraction pattern having at least ten characteristic peaks expressed in degrees 2-theta (± 0.2), selected from the group consisting of 10.08, 10.94, 16.58, 17.12, 17.53, 18.34, 18.66, 20.50, 21.14, 21.92, 22.22, 23.46, 26.22, 26.60, 27.72, and 30.3074, 10.940, =

9. — The polymorph of any one of the preceding claims, wherein the polymorph exhibits an X-ray powder diffraction pattern having peaks with 2-theta values substantially in accordance with Figure 3.

10. — The polymorph of any one of the preceding claims, wherein the polymorph exhibits an X-ray powder diffraction pattern having peaks with 2-theta values substantially in accordance with Table 3.

11. — The polymorph of any one of the preceding claims, wherein the polymorph exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of $^{\circ}\text{C}$ at a temperature of $228 \pm 5^{\circ}\text{C}$.

12. — The polymorph of any one of the preceding claims, wherein the polymorph exhibits a differential scanning calorimetry thermogram substantially in accordance with the lowermost plot shown in Figure 4, =

22, 12.0, 13. — The polymorph of any one of the preceding claims, wherein said polymorph is substantially free of impurities.

14. — The polymorph of any one of the preceding claims, wherein said polymorph is a crystalline solid substantially free of amorphous N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl-(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrochloride.

116, 13.318, 13.418, 13.541, 13.762, 13.899, 16.443, 16.583, 17.026, 17.124, 17.219, 17.53, 17.78, 18.032, 18.32, 18.340, 18.419, 18.66, 19.399, 20.182, 20.199, 20.421, 20.500, 20.839, 21.14, 21.84, 21.917, 21.958, 22.22, 22.499, 23.238, 23.46, 23.725, 24.159, 24.363, 24.7, 24.958, 25.498, 26.222, 26.596, 26.863, 27.72, 30.30, 30.557, and 30.879. ~~15.~~ 15. A method of preparing Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrochloride, comprising the step of combining N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide with hydrochloric acid.

~~16.2.~~ 16.2. The method of claim ~~15~~1, comprising the steps of:

- a)- Dissolving N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-~~4'~~4'-(morpholinomethyl)-[~~1,1'~~1,1']-biphenyl]-3-~~-~~carboxamide in a ~~first~~first solvent to obtain a solution;
- b)- Combining hydrochloric acid with the solution;
- c)- Combining a second solvent with the solution;
- d)- Precipitating or crystallizing ~~Polymorph C of N~~the solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-~~4'~~4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide monohydrochloride from the solution; and
- e)- Collecting ~~Polymorph C of N~~the solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl (tetrahydro-2H-pyran-4-yl)amino)-4-methyl-~~4'~~4'-(morpholinomethyl)-[~~1,1'~~1,1']-biphenyl]-3-carboxamide monohydrochloride.

~~17.3.~~ 17.3. The method of claim ~~16~~2, wherein the ~~first~~first solvent comprises ethanol.

~~18.4.~~ The method of claim ~~163~~, wherein the hydrochloric acid is in a concentrated aqueous solution.

~~19.5.~~ The method of claim ~~164~~, wherein the second solvent comprises ethyl acetate.

~~20.6.~~ The method of claim ~~165~~, wherein one or more of the solutions of steps a), b) or c) is heated.

~~21.— A pharmaceutical composition comprising a polymorph of any one of claims 1-14, and a pharmaceutically acceptable carrier or diluent.~~

~~22.7.~~ A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a ~~polymorph of any of claims 1-14 or a pharmaceutical composition of claim 21.~~

~~23.— The method of claim 22~~solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, or a salt thereof, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.083, 10.18, 10.74, 10.940, 11.22, 12.0, 13.116, 13.318, 13.418, 13.541, 13.762, 13.899, 16.443, 16.583, 17.026, 17.124, 17.219, 17.53, 17.78, 18.032, 18.32, 18.340, 18.419, 18.66, 19.399, 20.182, 20.199, 20.421, 20.500, 20.839, 21.14, 21.84, 21.917, 21.958, 22.22, 22.499, 23.238, 23.46, 23.725, 24.159, 24.363, 24.7, 24.958, 25.498, 26.222, 26.596, 26.863, 27.72, 30.30, 30.557, and 30.879, wherein the cancer is B cell lymphoma, non-Hodgkin's lymphoma, or breast cancer.

~~8. — The method of claim 7, wherein the cancer is non-Hodgkin's lymphoma.~~

9.24. The method of claim 7, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.

10. A method of inhibiting the histone methyltransferase activity of EZH2 in a subject in need thereof or in vitro, comprising administering to the subject an effective amount of a polymorph of any of claims 1-14 solid crystalline form of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, or a salt thereof, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.083, 10.18, 10.74, 10.940, 11.22, 12.0, 13.116, 13.318, 13.418, 13.541, 13.762, 13.899, 16.443, 16.583, 17.026, 17.124, 17.219, 17.53, 17.78, 18.032, 18.32, 18.340, 18.419, 18.66, 19.399, 20.182, 20.199, 20.421, 20.500, 20.839, 21.14, 21.84, 21.917, 21.958, 22.22, 22.499, 23.238, 23.46, 23.725, 24.159, 24.363, 24.7, 24.958, 25.498, 26.222, 26.596, 26.863, 27.72, 30.30, 30.557, and 30.879.

25.—A11. The method of inhibiting claim 10, wherein the histone methyltransferase activity of EZH2 in vitro comprising administering a polymorph of any of claims 1-14 is inhibited in a subject.

12. The method of claim 10, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.

13. The method of claim 1, wherein the solid crystalline form is Polymorph A of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph A exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/-

0.2), selected from the group consisting of 11.22, 12.0, 13.116, 13.418, 13.899, 17.026, 18.032, 18.32, 19.399, 20.199, 21.84, 22.499, 23.238, 24.363, 24.7, 24.958, 30.557, and 30.879.

14. The method of claim 1, wherein the solid crystalline form is Polymorph B of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph B exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.18, 10.74, 13.318, 13.541, 13.762, 16.443, 17.219, 17.78, 18.419, 20.182, 20.421, 20.839, 21.958, 23.725, 24.159, 25.498, and 26.863.

~~15. 26. — A pharmaceutical composition comprising a polymorph of any one of claims 1-14 for treating cancer.~~

~~27. — The pharmaceutical composition for treating cancer of claim 26, wherein the cancer is B cell lymphoma, non-Hodgkin's lymphoma or breast cancer.~~The method of claim 1, wherein the solid crystalline form is Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph C exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 10.083, 10.940, 16.583, 17.124, 17.534, 18.340, 18.662, 20.500, 21.143, 21.917, 22.219, 23.460, 26.222, 26.596, 27.722, and 30.299.

16. The method of claim 15, wherein the solid crystalline form exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 228 +/- 5 °C.

17. The method of claim 1, wherein the solid crystalline form exhibits an X-ray powder diffraction pattern having three or more characteristic peaks expressed in degrees 2-theta (+/- 0.2) at 17.53, 18.66, 21.14, 22.22, 23.46, 27.72 and 30.30.

18. The method of claim 7, wherein the solid crystalline form is Polymorph A of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph A exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 11.22, 12.0, 13.116, 13.418, 13.899, 17.026, 18.032, 18.32, 19.399, 20.199, 21.84, 22.499, 23.238, 24.363, 24.7, 24.958, 30.557, and 30.879.

19. The method of claim 7, wherein the solid crystalline form is Polymorph B of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph B exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.18, 10.74, 13.318, 13.541, 13.762, 16.443, 17.219, 17.78, 18.419, 20.182, 20.421, 20.839, 21.958, 23.725, 24.159, 25.498, and 26.863.

20. The method of claim 7, wherein the solid crystalline form is Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph C exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 10.083, 10.940, 16.583, 17.124, 17.534, 18.340, 18.662, 20.500, 21.143, 21.917, 22.219, 23.460, 26.222, 26.596, 27.722, and 30.299.

21. The method of claim 20, wherein the solid crystalline form exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 228 +/- 5 °C.

22. The method of claim 10, wherein the solid crystalline form is Polymorph A of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph A exhibits an

X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 11.22, 12.0, 13.116, 13.418, 13.899, 17.026, 18.032, 18.32, 19.399, 20.199, 21.84, 22.499, 23.238, 24.363, 24.7, 24.958, 30.557, and 30.879.

23. The method of claim 10, wherein the solid crystalline form is Polymorph B of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph B exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 8.438, 10.18, 10.74, 13.318, 13.541, 13.762, 16.443, 17.219, 17.78, 18.419, 20.182, 20.421, 20.839, 21.958, 23.725, 24.159, 25.498, and 26.863.

24. The method of claim 10, wherein the solid crystalline form is Polymorph C of N-((4,6-dimethyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-5-(ethyl(tetrahydro-2H-pyran-4-yl)amino)-4-methyl-4'-(morpholinomethyl)-[1,1'-biphenyl]-3-carboxamide, wherein Polymorph C exhibits an X-ray powder diffraction pattern having two or more peaks expressed in degrees 2-theta (+/- 0.2), selected from the group consisting of 10.083, 10.940, 16.583, 17.124, 17.534, 18.340, 18.662, 20.500, 21.143, 21.917, 22.219, 23.460, 26.222, 26.596, 27.722, and 30.299.

25. The method of claim 24, wherein the solid crystalline form exhibits a differential scanning calorimetry thermogram showing a primary endotherm expressed in units of °C at a temperature of 228 +/- 5 °C.