~~CLAIMS~~

~~What is claimed is:~~

CLAIMS

1. A crystalline form of {6-[(2-amino-3-chloropyridin-4-yl)sulfanyl]-3-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-methylpyrazin-2-yl}methanol, or a pharmaceutically acceptable salt thereof, characterized as Compound 1 Form D.

2. The crystalline form of claim 1, wherein ~~an X-ray powder diffraction pattern comprises 2θ values: about 18.48 and about 16.77~~the crystalline form is {6-[(2-amino-3-chloropyridin-4-yl)sulfanyl]-3-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-methylpyrazin-2-yl}methanol.

3. The crystalline form of claim 1, or a pharmaceutically acceptable salt thereof, wherein an X-ray powder diffraction pattern comprises 2θ values: about 18.48 and about 16.77.

4. The crystalline form of claim 2, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern further comprises one or more 2θ values ~~at~~selected from the group consisting of about~~:~~ 10.73, about 11.03, about 11.15, about 12.58, about 19.17, about 19.54, about 20.88, about 22.47, and about 25.59.

~~4~~5. The crystalline form of claim 1, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern is substantially in accordance with that shown in FIG. 10A.

~~5~~6. The crystalline form of ~~any one of claims~~claim 1~~-4~~, or a pharmaceutically acceptable salt thereof, wherein a differential scanning calorimetry (DSC) curve comprises an endotherm at about 51 °C, about 90 °C, or about 211 °C.

~~6~~7. The crystalline form of ~~any one of claims~~claim 1~~-4~~, or a pharmaceutically acceptable salt thereof, wherein the DSC curve is substantially as shown in FIG. 13~~.~~

7. The crystalline form of any one of claims 1-6, having the unit cell dimensions: a = 14.0679(4) Å, b = 16.0057(4) Å, c = 19.1837(6) Å, α = 90°, β = 90°, γ = 90°; cell volume (V) of 4319.5(2) Å^3; and a space group of $P2_12_12_1$ space group.

8. A crystalline form of {6-[(2-amino-3-chloropyridin-4-yl)sulfanyl]-3-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-methylpyrazin-2-yl}methanol, or a pharmaceutically acceptable salt thereof, characterized as Compound 1 Form B.

9. The crystalline form of claim 8, or a pharmaceutically acceptable salt thereof, wherein an X-ray powder diffraction pattern comprises 2θ values: about 20.0 and about 17.9.

10. The crystalline form of claim 9, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern further comprises one or more 2θ values atselected from the group consisting of about: 7.8, about 9.1, about 9.4, about 11.4, about 12.8, about 13.4, about 15.7, about 18.9, about 20.9, about 23.1, and about 25.0.

11. The crystalline form of claim 8, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern is substantially in accordance with that shown in FIG. 3A.

12. The crystalline form of any one of claimsclaim 8-11, or a pharmaceutically acceptable salt thereof, wherein a differential scanning calorimetry (the DSC) curve comprises an endotherm at about 188 °C and/or about 211°C. is substantially as shown in FIG. 6.

13. The crystalline form of any one of claims 8-11, wherein the DSC curve is substantially as shown in FIG. 6.

14. The crystalline form of any one of claims 8-11, having the unit cell dimensions: a = 9.65334(16) Å, b = 10.28825(18) Å, c = 11.62614(19) Å, α = 76.0621(15)°,

~~β = 89.6714(13)°, γ = 76.4043(15)°; cell volume (V) of 1087.68(3) Å³; and a space group of *P*1 space group.~~

~~15~~13. A crystalline form of {6-[(2-amino-3-chloropyridin-4-yl)sulfanyl]-3-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-methylpyrazin-2-yl}methanol, or a pharmaceutically acceptable salt thereof, characterized as Compound 1 Form C.

~~16~~14. The crystalline form of claim ~~15~~13, or a pharmaceutically acceptable salt thereof, wherein an X-ray powder diffraction pattern comprises 2θ values: about 18.56 and about 16.62.

~~17~~15. The crystalline form of claim ~~16~~14, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern further comprises one or more 2θ values ~~at~~ selected from the group consisting of about~~:~~ 10.78, about 11.11, about 12.29, about 19.06, about 19.57, about 20.83, and about 25.61.

~~18~~16. The crystalline form of claim ~~15~~13, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern is substantially in accordance with that shown in FIG. 8A.

~~19. The crystalline form of any one of claims 15-18, having the unit cell dimensions: *a* = 47.6458(8) Å, *b* = 14.4005(2) Å, *c* = 9.5460(2) Å, α = 90°, β = 90°, γ = 90°; cell volume (V) of 6549.8(2) Å³; and a space group of $P2_12_12_1$.~~

~~20~~17. A crystalline form of {6-[(2-amino-3-chloropyridin-4-yl)sulfanyl]-3-[(3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl]-5-methylpyrazin-2-yl}methanol, or a pharmaceutically acceptable salt thereof, characterized as Compound 1 Form A.

~~21~~18. The crystalline form of claim ~~20~~17, or a pharmaceutically acceptable salt thereof, wherein an X-ray powder diffraction pattern comprises 2θ values: about 16.66 and about 18.50.

2219. The crystalline form of claim 2118, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern further comprises one or more 2θ values at selected from the group consisting of about: 10.76, about 11.11, about 12.35, about 19.08, about 19.52, about 20.85, and about 25.63.

2320. The crystalline form of claim 2017, or a pharmaceutically acceptable salt thereof, wherein the X-ray powder diffraction pattern is substantially in accordance with that shown in FIG. 1A.

24. The21 A pharmaceutical composition comprising the crystalline form of claim 20, having an onset melting temperature of about 213 °C.

25. A pharmaceutical composition comprising the crystalline form of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2622. A pharmaceutical composition comprising the crystalline form of claim 25, wherein the pharmaceutical composition comprises Compound 1 Form D8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2723. A pharmaceutical composition comprising the crystalline form of claim 25, wherein the pharmaceutical composition comprises Compound 1 Form C13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2824. A pharmaceutical composition comprising a crystalline form of claim 25, wherein the pharmaceutical composition comprises Compound 1 Form B17, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2925. A pharmaceutical composition of claim 2521, wherein the pharmaceutical composition further comprises Compound 1 Form A,one or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~30. A pharmaceutical composition of claim 25, wherein the pharmaceutical composition comprises at least two~~more crystalline forms selected from the group consisting of

Compound 1 Form A, or a pharmaceutically acceptable salt thereof,

Compound 1 Form B, or a pharmaceutically acceptable salt thereof, and

Compound 1 Form C, or a pharmaceutically acceptable salt thereof;

and a pharmaceutically acceptable carrier.

26. Use of an effective amount of the crystalline form of claim 1, or a pharmaceutically acceptable salt thereof, ~~and~~

~~Compound 1 Form D, or a pharmaceutically acceptable salt thereof,~~

~~and a pharmaceutically acceptable carrier.~~

~~31. A pharmaceutical composition of claim 25, wherein~~in the ~~pharmaceutical composition comprises Compound 1 Form D, or a pharmaceutically acceptable salt thereof, and Compound 1 Form A, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.~~

~~32. A pharmaceutical composition of claim 25, wherein the pharmaceutical composition comprises Compound 1 Form D, or a pharmaceutically acceptable salt thereof, and Compound 1 Form B, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.~~

~~33. A pharmaceutical composition of claim 25, wherein the pharmaceutical composition comprises Compound 1 Form D, or a pharmaceutically acceptable salt thereof, and Compound 1 Form C, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.~~

~~34. A method of~~manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof~~, comprising administering to the subject an effective amount the crystalline form of any one of claims 1-24, or a pharmaceutically acceptable salt thereof.~~

~~35. The method of claim 34~~, wherein the disease is selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

~~36. A crystalline form of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, for use as a medicament.~~

~~37. A crystalline form of any one of claims 1-24, or a pharmaceutically acceptable salt thereof, for use in treating or preventing a disease associated with SHP2 modulation.~~

~~38~~27. Use of ~~a~~an effective amount of the crystalline form of ~~any one of claims 1-24~~claim 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating ~~or preventing a disease associated with SHP2 modulation.~~

~~39. A method of treating~~ a disease associated with SHP2 modulation in a subject in need thereof, ~~comprising administering to the subject an effective amount of a pharmaceutical composition of any one of claims 25-33~~wherein the disease is selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

~~40. The method of claim 39~~28. Use of an effective amount of the crystalline form of claim 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof, wherein the disease is selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

41. A pharmaceutical composition of any one29. Use of an effective amount of claims 25-33 for use as the crystalline form of claim 17, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament.

42. A pharmaceutical composition of any one of claims 25-33 for use in for treating or preventing a disease associated with SHP2 modulation in a subject in need thereof, wherein the disease is selected from Noonan Syndrome, Leopard Syndrome, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, acute myeloid leukemia and cancers of the breast, lung and colon.

4330. Use of a pharmaceutical composition of any onean effective amount of claims 25-33the crystalline form of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof, wherein the disease is selected from esophageal cancer, gastric carcinoma, anaplastic large-cell lymphoma, and glioblastoma.

31. Use of an effective amount of the crystalline form of claim 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing a disease associated with SHP2 modulation. in a subject in need thereof, wherein the disease is selected from esophageal cancer, gastric carcinoma, anaplastic large-cell lymphoma, and glioblastoma.

32. Use of an effective amount of the crystalline form of claim 13, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease associated with SHP2 modulation in a subject in need thereof, wherein the disease is selected from esophageal cancer, gastric carcinoma, anaplastic large-cell lymphoma, and glioblastoma.

33. Use of an effective amount of the crystalline form of claim 17, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease associated with

SHP2 modulation in a subject in need thereof, wherein the disease is selected from esophageal cancer, gastric carcinoma, anaplastic large-cell lymphoma, and glioblastoma.