

WHAT IS CLAIMED IS:

1. A crystalline polymorph form of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one, or a hydrate thereof.
2. The crystalline polymorph form of claim 1, wherein the crystalline form is a polymorph form of the free base of (7*S*,13*R*)-11-fluoro-7,13-dimethyl-6,7,13,14-tetrahydro-1,15-ethenopyrazolo[4,3-*f*][1,4,8,10]benzoxatriazacyclotridecin-4(5*H*)-one, or a hydrate thereof.
3. The crystalline polymorph of claim 1 or 2, wherein the crystalline form is a monohydrate.
4. The crystalline polymorph of claim 1 or 2, wherein the crystalline form is anhydrous.
5. A crystalline polymorph form A of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one having a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 20.1 ± 0.1 .
6. The crystalline polymorph form of claim 5, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 11.3 ± 0.1 and 20.1 ± 0.1 .
7. The crystalline polymorph form of claim 6, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 11.3 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 .
8. The crystalline polymorph form of claim 7, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 11.3 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 .
9. The crystalline polymorph form of claim 8, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 10.3 ± 0.1 , 11.3 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 .

10. The crystalline polymorph form of claim 9, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 10.3 ± 0.1 , 11.3 ± 0.1 , 16.6 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , and 23.9 ± 0.1 .
11. The crystalline polymorph form of claim 10, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 10.3 ± 0.1 , 11.3 ± 0.1 , 16.6 ± 0.1 , 18.0 ± 0.1 , 20.1 ± 0.1 , 20.5 ± 0.1 , and 23.9 ± 0.1 .
12. A crystalline polymorph form D of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one having, a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 18.8 ± 0.1 .
13. The crystalline polymorph form of claim 12, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 18.8 ± 0.1 and 20.9 ± 0.1 .
14. The crystalline polymorph form of claim 13, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 12.3 ± 0.1 , 18.8 ± 0.1 , and 20.9 ± 0.1 .
15. The crystalline polymorph form of claim 14, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 12.3 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 .
16. The crystalline polymorph form of claim 15, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 12.3 ± 0.1 , 13.1 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 .
17. The crystalline polymorph form of claim 16, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 12.3 ± 0.1 , 13.1 ± 0.1 , 15.3 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 .

18. The crystalline polymorph form of claim 17, wherein the crystalline polymorph form has a powder X-ray diffraction pattern comprising a peak at diffraction angle (2θ) of 9.4 ± 0.1 , 12.3 ± 0.1 , 13.1 ± 0.1 , 15.3 ± 0.1 , 18.8 ± 0.1 , 19.4 ± 0.1 , and 20.9 ± 0.1 .

19. A crystalline polymorph form of any one of claims 1 to 11, having a Raman spectra comprising at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or at least about 8 peaks selected from Table 3.

20. A crystalline polymorph form of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 1.

21. A crystalline polymorph form of (3a*R*,11*S*,20a*S*)-7-fluoro-11-methyl-2,3,3a,12,13,20a-hexahydro-1*H*,5*H*-17,19-(metheno)cyclopenta[5,6][1,4]oxazino[3,4-*i*]pyrazolo[4,3-*f*]pyrido[3,2-*l*][1,4,8,10]oxatriazacyclotridecin-14(11*H*)-one having a powder X-ray diffraction pattern substantially the same as shown in FIG. 3.

22. A pharmaceutical composition comprising the crystalline polymorph form of any one of the preceding claims.

23. A method of treating disease in a mammal, the method comprising administering to the mammal a therapeutically effective amount of the crystalline polymorph form of any one of claims 1 to 21.

24. The method of claim 23, wherein the mammal is a human.

25. The method of claim 24, wherein the disease is selected from the group consisting of cancer, pain, neurological diseases, autoimmune diseases, and inflammation.

26. The method of claim 25, wherein the disease is cancer.

27. The method of claim 26, wherein the cancer is selected from the groups consisting of lung cancer, non-small cell lung cancer, small cell lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, hepatocellular carcinoma, cutaneous or intraocular

melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, gastric and esophago-gastric cancers, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, such as anaplastic large cell lymphoma, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), glioblastoma, primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, inflammatory myofibroblastic tumors, and combinations thereof.

28. The method of any one of claims 23-27, wherein the disease is cancer mediated by a genetically altered RET.

29. The method of any one of claims 23-27, wherein the disease is cancer mediated by a genetically altered RET comprising at least one point mutation selected from the group consisting of A883F, E762Q, G691S, L790F, M918T, R749T, R813Q, S891A, S904A, S904F, V778I, V804L, V804M, Y791F, and Y806H.

30. The method of any one of claims 23-27, wherein the disease is cancer mediated by a fusion protein comprising a fragment of a protein encoded by an RET gene and a fragment of a protein which can form coiled-coil interaction to facilitate the protein dimerization or oligomerization.

31. The method of any one of claims 23-27, wherein the disease is cancer mediated by a fusion protein comprising a fragment of a protein encoded by an RET gene and a fragment of a protein encoded by a gene selected from the group consisting of KIF5B, CCDC6, NCOA4, TRIM24, TRIM33, PRKAR1A, GOLGA5, KTN1, ERC1, MBD1, and TRIM27.

32. The method of claim 31, wherein the fusion protein comprises a fragment of a protein encoded by an RET gene and a fragment of a protein encoded by a KIF5B gene.

33. The method of claim 28, wherein the genetically altered RET is a KIF5B-RET, CCDC6-RET, NCOA4-RET, TRIM24-RET, TRIM33-RET, PRKAR1A-RET, GOLGA5-RET, KTN1-RET, ERC1-RET, MBD1-RET, or TRIM27-RET fusion protein.

34. The method of claim 28 or 33, wherein the genetically altered RET is a KIF5B-RET fusion protein.

35. The method of claim 28, 33, or 34, wherein the KIF5B-RET fusion protein is a wild-type protein.

36. The method of claim 28, 33, or 34, wherein the KIF5B-RET fusion protein comprises at least one resistance mutation.

37. The method of claim 28, 33, or 34, wherein the KIF5B-RET fusion protein comprises at least one gate keeper resistance mutation.

38. The method of claim 28, 33, or 34, wherein the KIF5B-RET fusion protein comprises at least one solvent front resistance mutation.

39. The method of claim 28, 33, or 34, wherein the KIF5B-RET fusion protein comprises at least one mutation selected from the group consisting of A883F, E762Q, G691S, L790F, M918T, R749T, R813Q, S891A, S904A, S904F, V778I, V804L, V804M, Y791F, Y806H, V804M, G810R, G810C, and G810S.

40. The method of claim 28, 33, or 34, wherein the KIF5B-RET fusion protein comprises at least one mutation selected from the group consisting of V804M, G810R, G810C, and G810S.