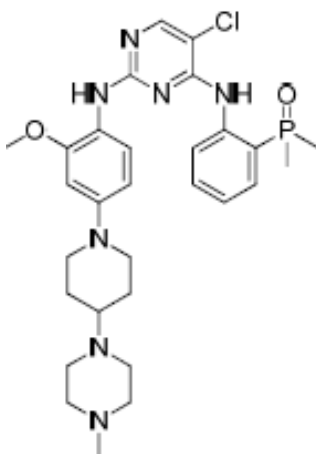


CRYSTALLINE FORMS OF 5-CHLORO-N4-[2-(DIMETHYLPHOSPHORYL)PHENYL]-N2-{2-METHOXY-4-[4-(4-METHYLPYPERAZIN-1-YL)PIPERIDIN-1-YL]PHENYL} PYRIMIDINE-2,4-DIAMINE

[0001] This application is directed to novel crystalline forms of 5-chloro-N4-[2-(dimethylphosphoryl)phenyl]-N2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]pyrimidine-2,4-diamine (also referred to as, “AP26113” and “brigatinib”), compositions comprising such crystalline forms, and methods of their preparation and use.

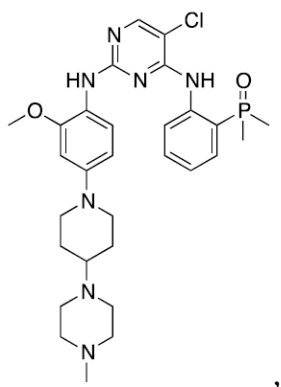
[0002] Brigatinib has the chemical formula $C_{29}H_{39}ClN_7O_2P$ which corresponds to a formula weight of 584.09 g/mol. Its chemical structure is shown below:



[0003] Brigatinib is a multi-targeted tyrosine-kinase inhibitor useful for the treatment of non-small cell lung cancer (NSCLC) and other diseases. It is a potent inhibitor of ALK (anaplastic lymphoma kinase) and is in clinical development for the treatment of adult patients with ALK-driven NSCLC. Crizotinib (XALKORI[®]) is an FDA approved drug for first-line treatment of ALK-positive NSCLC. “Despite initial responses to crizotinib, the majority of patients have a relapse within 12 months, owing to the development of resistance.” Shaw et al., *New Eng. J. Med.* 370:1189-97 2014. Thus, a growing population of cancer patients are in need of new and effective therapies for ALK-positive cancers.

CLAIMS

1. A crystalline form of brigatinib having the structure:

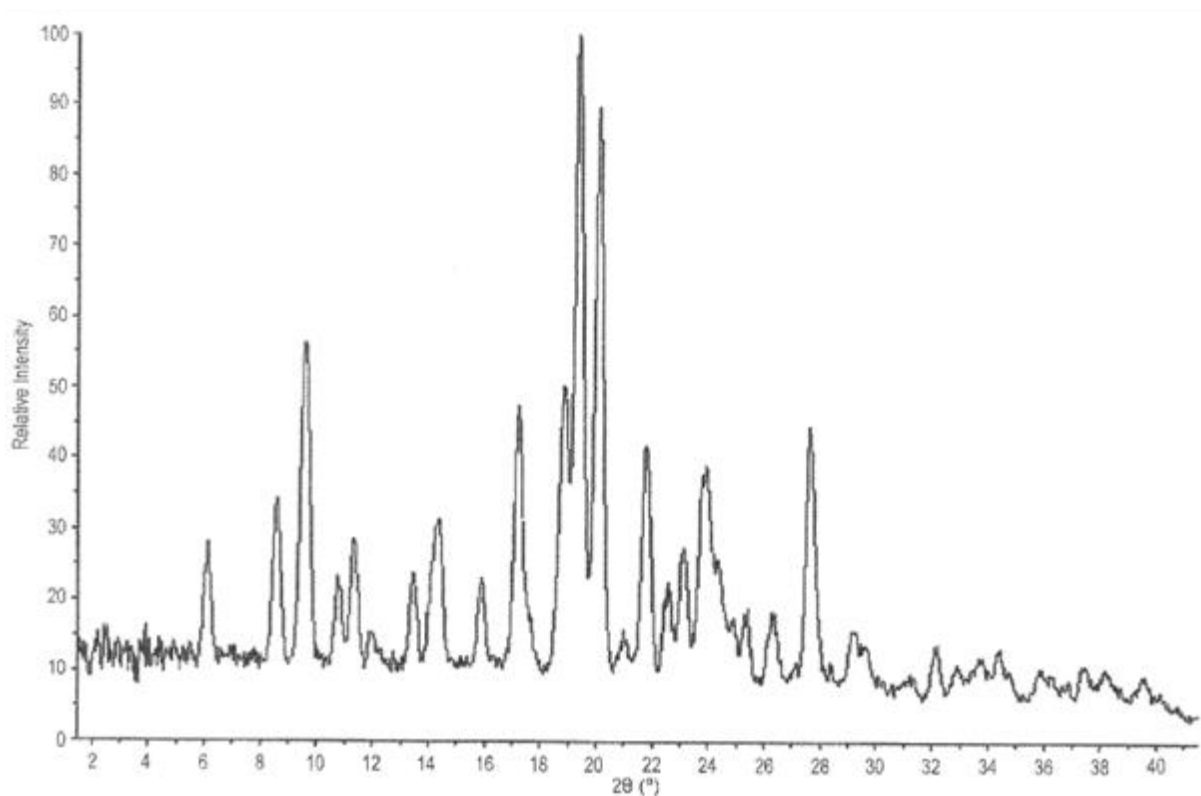


which is crystalline Form A characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 6.1, 8.6, 9.6, 10.8, 11.3, 13.5, 14.3, 15.9, 17.2, 18.9, 19.4, 20.1, 21.8, 22.6, 23.1, 23.9, and 27.7 °2θ, with a variance of ±0.3 °2θ.

2. The crystalline form of claim 1, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 9.6, 17.2, 19.4, 20.1, 23.1, and 27.7 °2θ, with a variance of ±0.3 °2θ.

3. The crystalline form of claim 1, which is characterized by an X-ray powder diffraction pattern having peaks at 9.6, 17.2, 19.4, 20.1, 23.1, and 27.7 °2θ, with a variance of ±0.3 °2θ.

4. The crystalline form of claim 1, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:

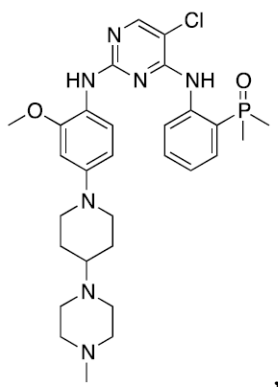


5. The crystalline form of any one of claims 1–4, which is anhydrous.
6. The crystalline form of any one of claims 1–5, having an onset melting temperature of 214.5 °C.
7. The crystalline form of any one of claims 1–6, having a FT-IR spectrum with at least one of the following frequency bands:

Frequency (cm⁻¹)
3241.0,
3165.1,
2980.0 to 2793.2,
1616.4 to 1417.6,
1441.1 to 1219.8,
1354.6 to 1278.0,
1307.4 to 1196.1,
1163.6 to 1135.0,
1094.9 to 794.6,
867.4, and
768.6 to 716.8.

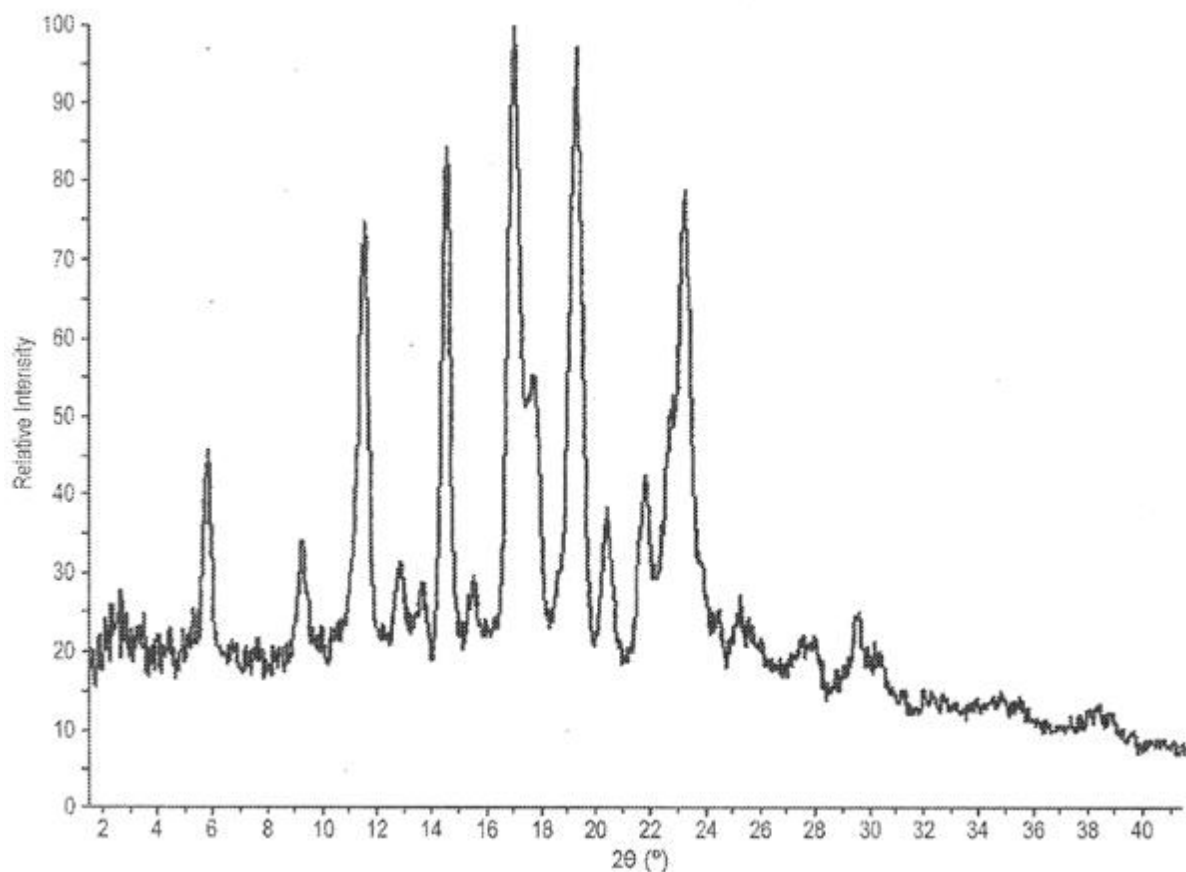
8. The crystalline form of any one of claims 1–7, which is not hygroscopic.

9. The crystalline form of any one of claims 1–8, which exhibits a weight loss of 0.23% upon heating from 30 °C to 100 °C.
10. The crystalline form of any one of claims 1–9, having unit cell dimensions of: $a = 9.6$ Å, $b = 10.8$ Å, $c = 15.0$ Å, $\alpha = 76^\circ$, $\beta = 80^\circ$, and $\gamma = 74^\circ$.
11. A process for preparing the crystalline form of claim 1, comprising elevating the temperature of crystallization to 60 °C and adding an NaOH solution at a slow rate.
12. A crystalline form of brigatinib having the structure:

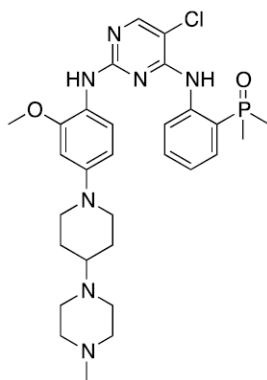


which is crystalline Form B characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 5.7, 9.2, 11.5, 12.8, 14.5, 15.5, 16.9, 17.7, 19.2, 20.4, 21.8, 23.2, and 29.5 °2θ, with a variance of ±0.3 °2θ.

13. The crystalline form of claim 12, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 11.5, 14.5, 16.9, 19.2, and 23.2 °2θ, with a variance of ±0.3 °2θ.
14. The crystalline form of claim 12, which is characterized by an X-ray powder diffraction pattern having peaks at 11.5, 14.5, 16.9, 19.2, and 23.2 °2θ, with a variance of ±0.3 °2θ.
15. The crystalline form of claim 12, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



16. A crystalline form of brigatinib having the structure:

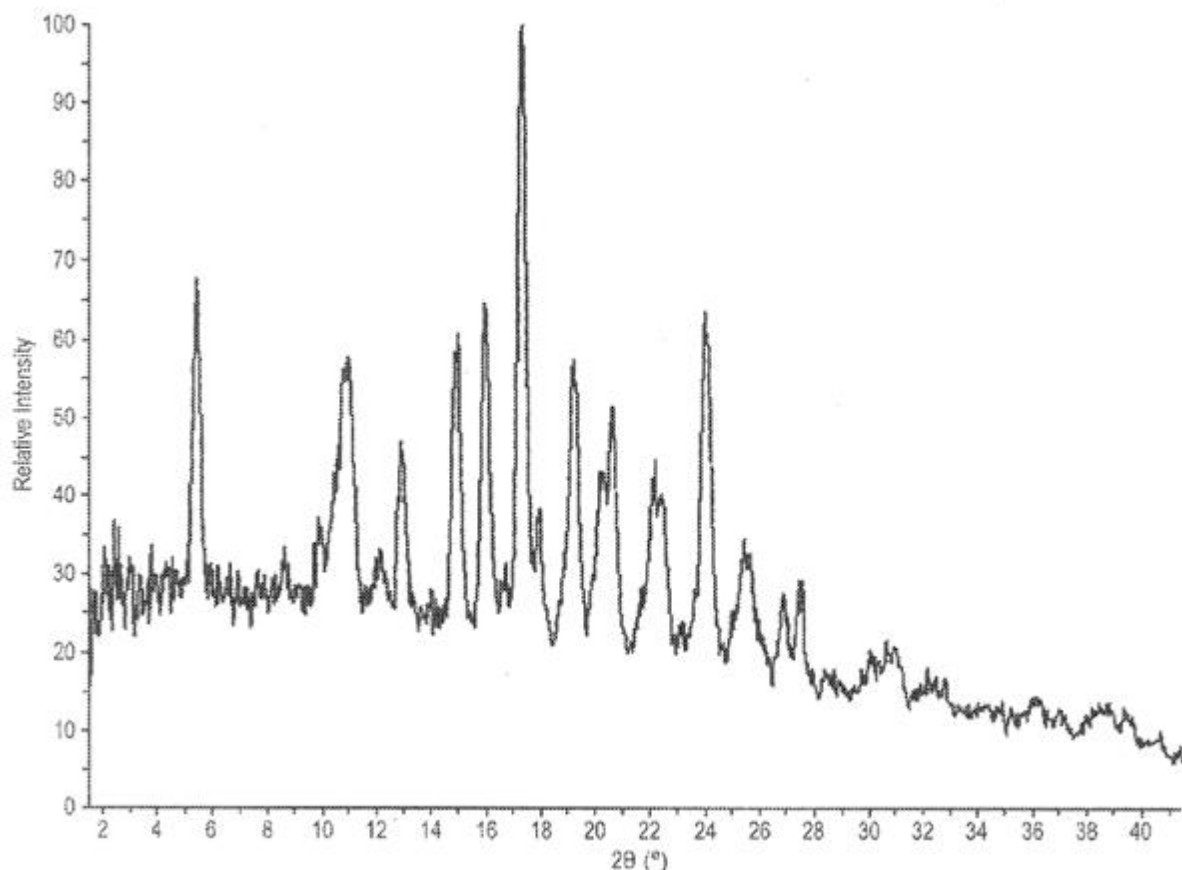


which is crystalline Form C characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 2.1, 2.5, 5.4, 9.9, 10.9, 12.9, 14.9, 15.9, 16.6, 17.3, 17.9, 19.2, 20.6, 23.9, 26.8, and 27.4 °2θ, with a variance of ±0.3 °2θ.

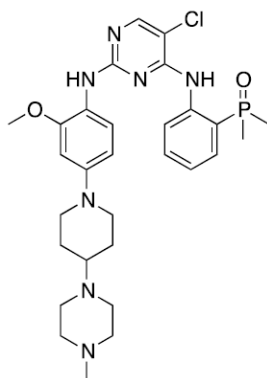
17. The crystalline form of claim 16, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 5.4, 14.9, 15.9, 17.3, 19.2, and 23.9 °2θ, with a variance of ±0.3 °2θ.

18. The crystalline form of claim 16, which is characterized by an X-ray powder diffraction pattern having peaks at 5.4, 14.9, 15.9, 17.3, 19.2, and 23.9 °2θ, with a variance of ±0.3 °2θ.

19. The crystalline form of claim 16, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



20. A crystalline form of brigatinib having the structure:



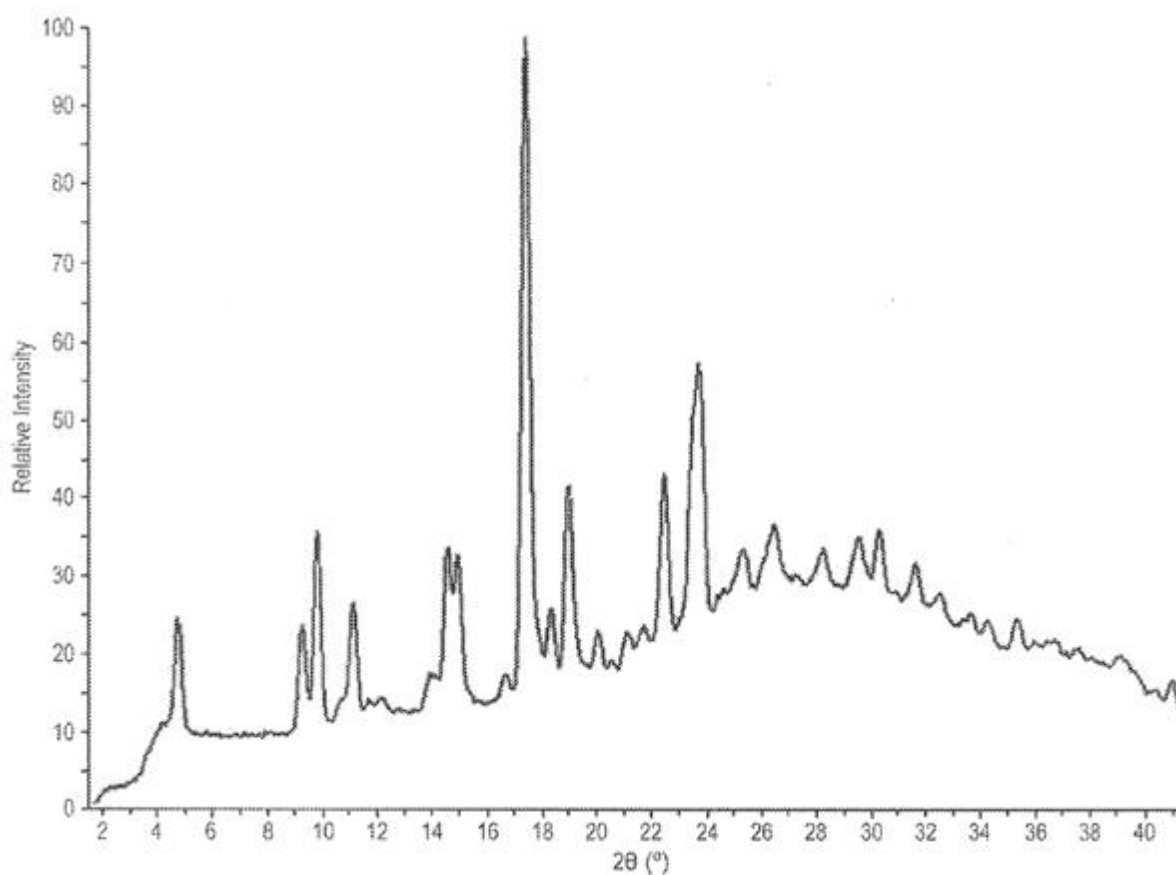
which is crystalline Form D characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 4.7, 9.2, 9.7, 11.1, 14.5, 17.4, 18.9, 22.4, and 23.7 °2θ, with a

variance of $\pm 0.3^\circ 2\theta$.

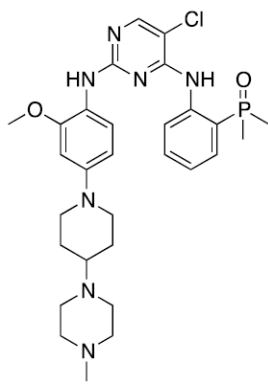
21. The crystalline form of claim 20, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 9.7, 11.1, 17.4, 18.9, and $23.7^\circ 2\theta$, with a variance of $\pm 0.3^\circ 2\theta$.

22. The crystalline form of claim 20, which is characterized by an X-ray powder diffraction pattern having peaks at 9.7, 11.1, 17.4, 18.9, and $23.7^\circ 2\theta$, with a variance of $\pm 0.3^\circ 2\theta$.

23. The crystalline form of claim 20, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



24. A crystalline form of brigatinib having the structure:

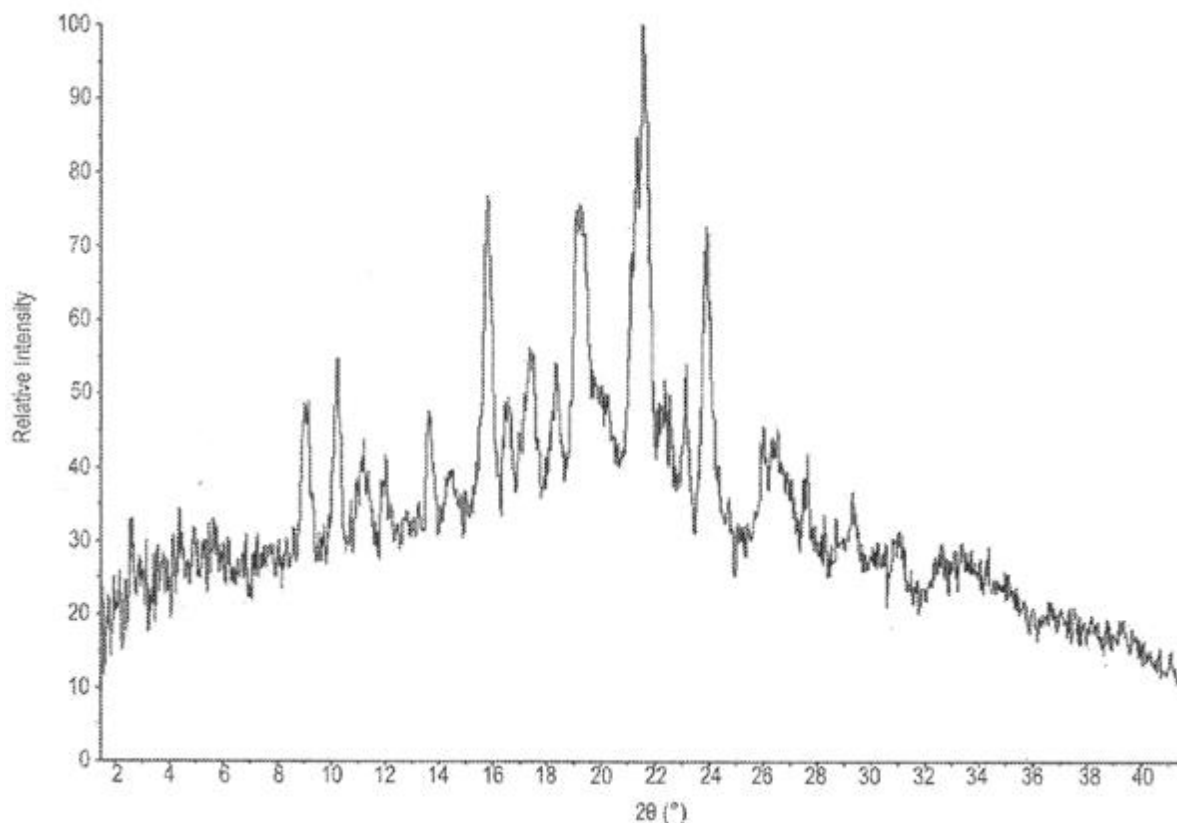


which is crystalline Form E characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 9.1, 10.2, 11.2, 12.0, 13.7, 14.4, 15.8, 16.5, 17.4, 18.3, 19.2, 21.6, 22.3, 23.1, 23.9, 26.0, 26.4, 25.8, and 29.3 °2θ, with a variance of ±0.3 °2θ.

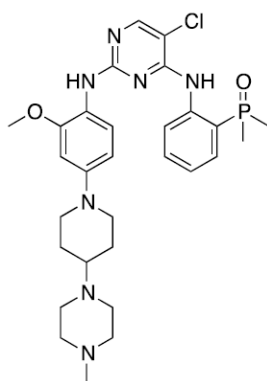
25. The crystalline form of claim 24, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 9.1, 10.2, 15.8, 19.2, and 23.9 °2θ, with a variance of ±0.3 °2θ.

26. The crystalline form of claim 24, which is characterized by an X-ray powder diffraction pattern having peaks at 9.1, 10.2, 15.8, 19.2, and 23.9 °2θ, with a variance of ±0.3 °2θ.

27. The crystalline form of claim 24, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



28. A crystalline form of brigatinib having the structure:



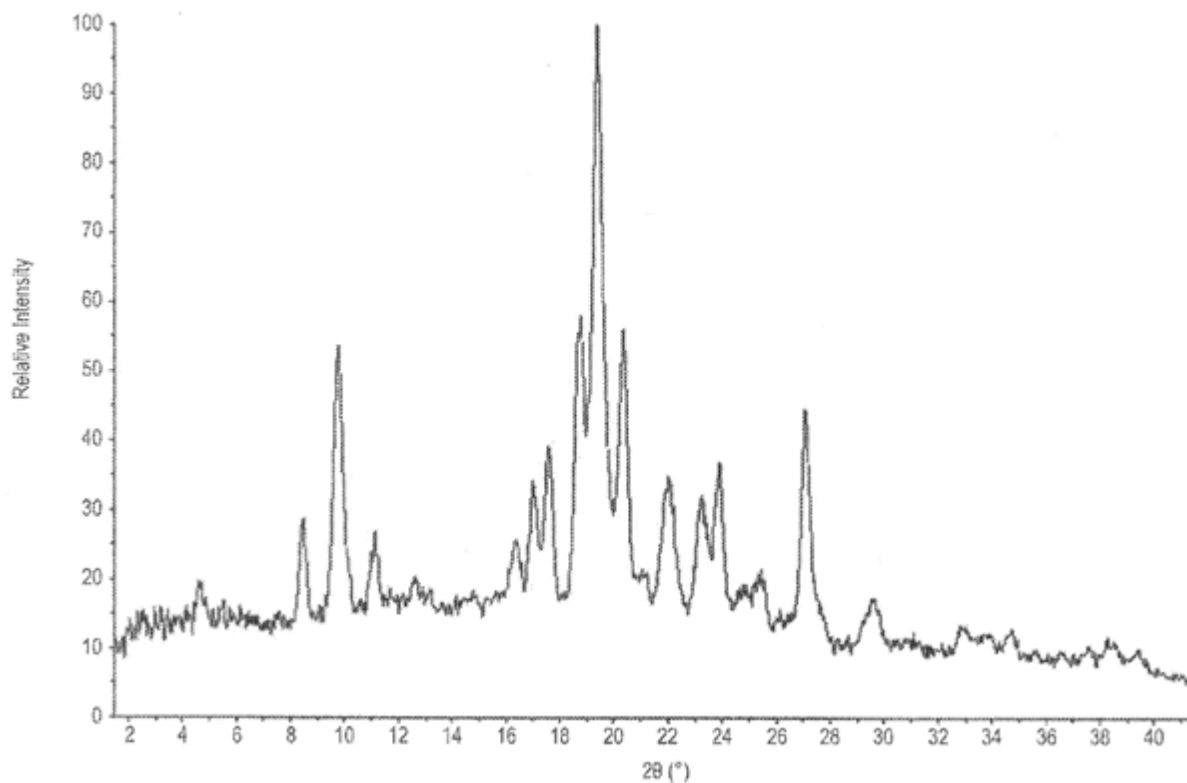
which is crystalline Form F characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 8.5, 9.8, 11.1, 16.3, 17.0, 17.6, 18.7, 19.4, 20.3, 22.0, 23.2, 23.9, and 27.1 °2θ, with a variance of ±0.3 °2θ.

29. The crystalline form of claim 28, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 9.8, 17.0, 19.4, 20.3, and 27.1 °2θ, with a variance of ±0.3 °2θ.

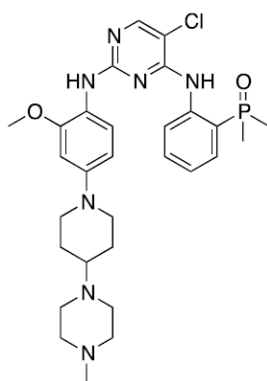
30. The crystalline form of claim 28, which is characterized by an X-ray powder

diffraction pattern having peaks at 9.8, 17.0, 19.4, 20.3, and 27.1 °2θ, with a variance of ±0.3 °2θ.

31. The crystalline form of claim 28, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



32. A crystalline form of brigatinib having the structure:



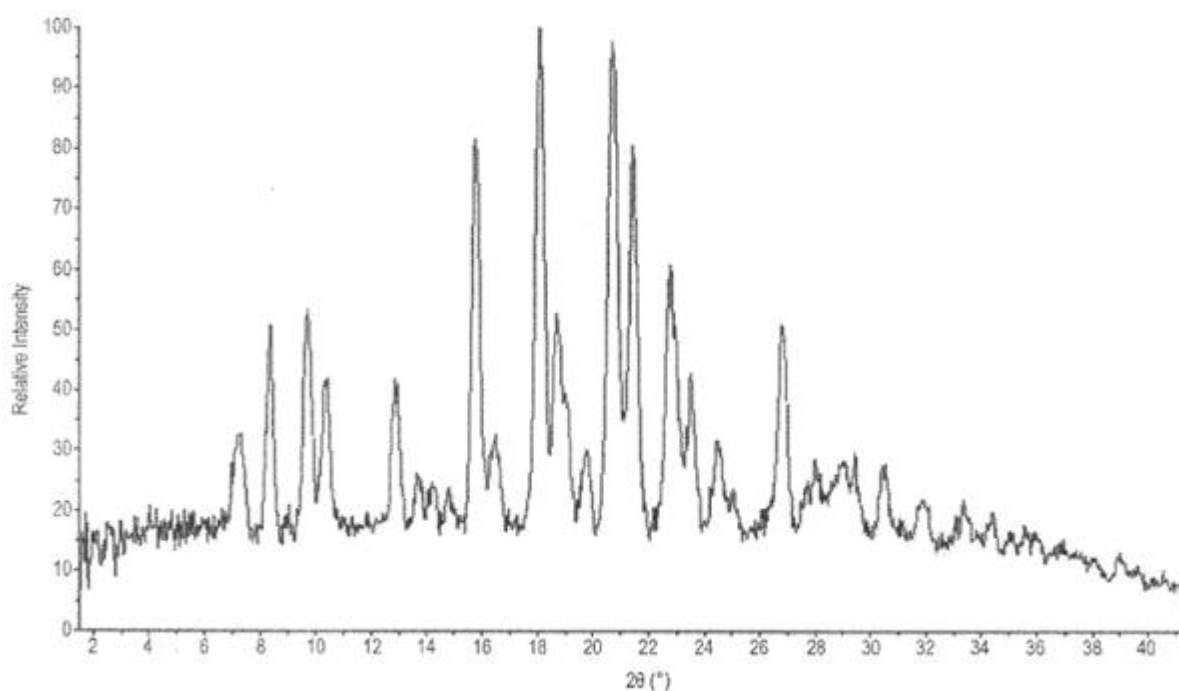
which is crystalline Form G characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 7.2, 8.3, 9.7, 10.4, 12.9, 15.8, 18.1, 18.7, 20.7, 21.5, 22.8, 23.5, 24.5, and 26.8 °2θ, with a variance of ±0.3 °2θ.

33. The crystalline form of claim 32, which is characterized by an X-ray powder

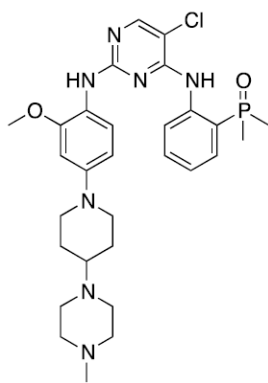
diffraction pattern having at least two peaks chosen from 8.3, 9.7, 12.9, 15.8, 18.1, 20.7, 22.8, and 26.8 °2θ, with a variance of ±0.3 °2θ.

34. The crystalline form of claim 32, which is characterized by an X-ray powder diffraction pattern having peaks at 8.3, 9.7, 12.9, 15.8, 18.1, 20.7, 22.8, and 26.8 °2θ, with a variance of ±0.3 °2θ.

35. The crystalline form of claim 32, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



36. A crystalline form of brigatinib having the structure:

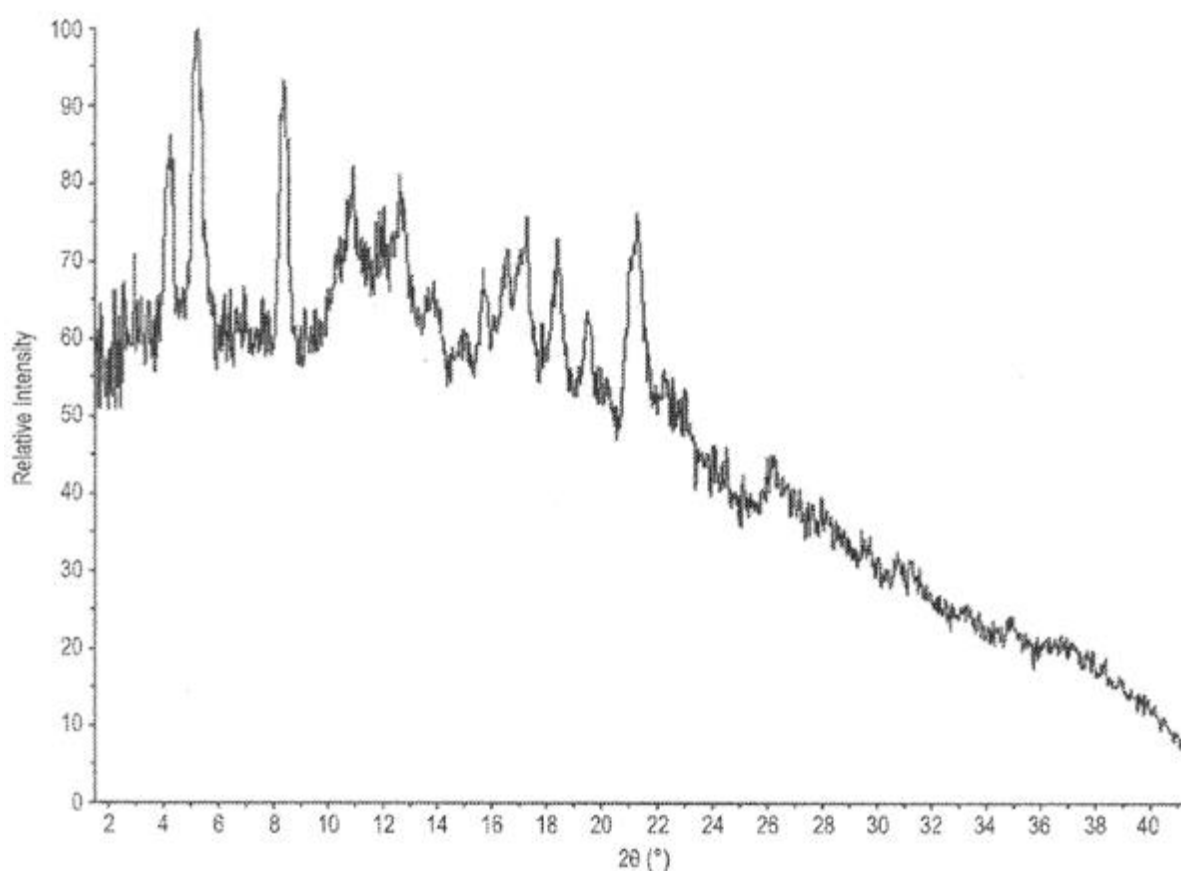


which is crystalline Form H characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 4.2, 5.2, 8.4, 10.9, 12.7, 15.0, 15.7, 16.5, 17.2, 18.4, 19.5, and 21.3 °2θ, with a variance of ±0.3 °2θ.

37. The crystalline form of claim 36, which is characterized by an X-ray powder diffraction pattern having at least two peaks chosen from 4.2, 5.2, 8.4, 10.9, 12.7, and 21.3 °2θ, with a variance of ±0.3 °2θ.

38. The crystalline form of claim 36, which is characterized by an X-ray powder diffraction pattern having peaks at 4.2, 5.2, 8.4, 10.9, 12.7, and 21.3 °2θ, with a variance of ±0.3 °2θ.

39. The crystalline form of claim 36, which is characterized by an X-ray powder diffraction pattern substantially as shown in the X-ray powder diffraction pattern:



40. A pharmaceutical composition comprising at least one crystalline form of brigatinib of any one of claims 1–39, and at least one component chosen from the group consisting of pharmaceutically acceptable carriers, pharmaceutically acceptable vehicles, and pharmaceutically acceptable excipients.

41. The pharmaceutical composition of claim 40, wherein the at least one crystalline form of brigatinib is Form A.

42. Use of at least one crystalline form of brigatinib of any one of claims 1–39 for the manufacture of a medicament for treating non-small cell lung cancer.
43. The use of claim 42, wherein the at least one crystalline form of brigatinib is Form A.