

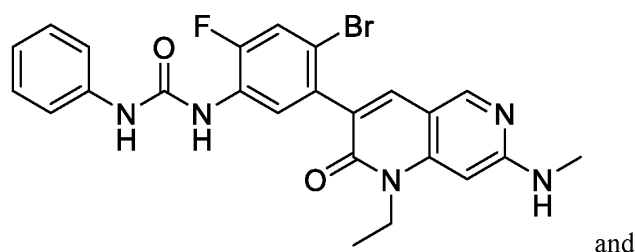
CLAIMS

What is claimed is:

1. A pharmaceutically acceptable composition for oral administration, the composition comprising:

5 (i) a solid dispersion, wherein the solid dispersion comprises:

the amorphous form of a compound represented by Formula (I):



Formula (I)

a pharmaceutically acceptable polymer; and

10 (ii) one or more pharmaceutically acceptable excipients.

2. The pharmaceutically acceptable composition of claim 1, wherein the solid dispersion has no more than about 5% w/w of any crystalline form of the compound.

3. The pharmaceutically acceptable composition of claim 1 or 2, wherein the solid dispersion has substantially no detectable amount of any crystalline form of the compound.

15 4. The pharmaceutically acceptable composition of any one of claims 1-3, wherein the amorphous form has a powder X-ray diffraction pattern substantially as shown in Figure 1.

5. The pharmaceutically acceptable composition of any one of claims 1-4, wherein the composition contains not more than about 5% (w/w) of any crystalline form of the compound in the aggregate when exposed to 60% relative humidity at 25 °C for 1 month, 3 months or 6
20 months.

6. The pharmaceutically acceptable composition of any one of claims 1-4, wherein the composition contains not more than about 5% (w/w) of any crystalline form of the compound in the aggregate when exposed to 75% relative humidity at 40 °C for 1 month, 3 months or 6 months.

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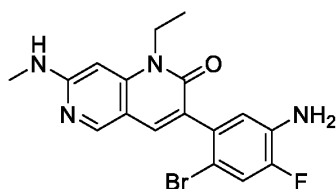
7. The pharmaceutically acceptable composition of any one of claims 1-6 comprising about 10% to about 30% by weight of the compound based on the total weight of the solid dispersion.
8. The pharmaceutically acceptable composition of any one of claims 1-7, comprising about 20% to about 30% by weight of the compound based on the total weight of the solid dispersion.
9. The pharmaceutically acceptable composition of any one of claims 1-8, comprising about 25% by weight of the compound based on the total weight of the solid dispersion.
10. The pharmaceutically acceptable composition of any one of claims 1-9, wherein the pharmaceutically acceptable polymer is selected from the group consisting of: polyvinyl pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin, hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate, dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, hydroxyethyl cellulose, methyl cellulose and hydroxy propyl cellulose, poly methacrylic acid-ethyl acrylate, poly methacrylic acid-methyl methacrylate, poly methyl methacrylate-ethyl acrylate, poly trimethylammonioethyl methacrylate chloride-methyl methacrylate-ethyl acrylate and

poly(butylmethacrylate-co-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate), and mixtures thereof.

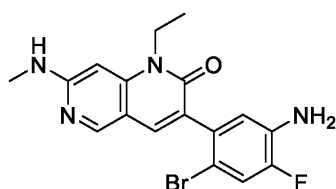
11. The pharmaceutically acceptable composition of any one of claims 1-10, wherein the pharmaceutically acceptable polymer is selected from the group consisting of: polyvinyl
 5 pyrrolidone, polyethyleneoxide, polyethylene glycol, poly(vinyl pyrrolidone-co-vinyl acetate), polyoxyethylene-polyoxypropylene block copolymers, graft copolymers comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate, polymethacrylates, polyoxyethylene alkyl ethers, polyoxyethylene castor oils, polycaprolactam, polylactic acid, polyglycolic acid, poly(lactic-glycolic)acid, lipids, cellulose, pullulan, dextran, maltodextrin,
 10 hyaluronic acid, polysialic acid, chondroitin sulfate, heparin, fucoidan, pentosan polysulfate, spirulan, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose propionate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate, cellulose acetate isophthalate,
 15 carboxymethyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate phthalate, hydroxypropyl methylcellulose propionate phthalate, hydroxypropyl methylcellulose acetate trimellitate, hydroxypropyl methylcellulose propionate trimellitate, cellulose acetate succinate, methyl cellulose acetate succinate, dextran, dextran acetate, dextran propionate, dextran succinate, dextran acetate propionate,
 20 dextran acetate succinate, dextran propionate succinate, dextran acetate propionate succinate, poly(methacrylic acid-co-methyl methacrylate) 1:1, poly(methacrylic acid-co-methyl methacrylate) 1:2, poly(methacrylic acid-co-ethyl acrylate) 1:1, and mixtures thereof.

12. The pharmaceutically acceptable composition of any one of claims 1-11, wherein the pharmaceutically acceptable polymer is hydroxypropyl methyl cellulose acetate succinate.
- 25 13. The pharmaceutically acceptable composition of any one of claims 1-12, wherein the compound and the pharmaceutically acceptable polymer are present in a ratio of compound:polymer from about 40:60 to about 10:90.
14. The pharmaceutically acceptable composition of any one of claims 1-13, wherein the compound and the pharmaceutically acceptable polymer are present in a ratio of
 30 compound:polymer from about 30:70 to about 20:80.

15. The pharmaceutically acceptable composition of any one of claims 1-14, wherein the compound and the pharmaceutically acceptable polymer are present in a ratio of compound:polymer of about 25:75.
16. The pharmaceutically acceptable composition of anyone of claims 1-15, wherein the solid dispersion is a solid spray-dried dispersion.
17. The pharmaceutically acceptable composition of any one of claims 1-16, wherein the solid dispersion has a solubility in water at pH 6.5 of about 120 μ g/mL at 25 °C.
18. The pharmaceutically acceptable composition of any one of claims 1-17, wherein the solid dispersion has a solubility in water at pH 2 of about 178 μ g/mL at 25 °C.
19. The pharmaceutically acceptable composition of any one of claims 1-18, comprising less than about 10 % by weight of a compound represented by Formula (II):

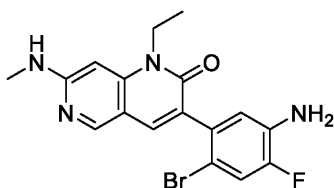
**Formula (II)**

- based on the weight of the compound of Formula (I).
20. The pharmaceutically acceptable composition of any one of claims 1-19, comprising less than about 3 % by weight of a compound represented by Formula (II):

**Formula (II)**

- based on the weight of the compound of Formula (I).
- 20

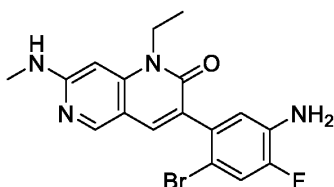
21. The pharmaceutically acceptable composition of any one of claims 1-20, comprising less than about 1 % by weight of a compound represented by Formula (II):



Formula (II)

5 based on the weight of the compound of Formula (I).

22. The pharmaceutically acceptable composition of any one of claims 1-21, comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (II):

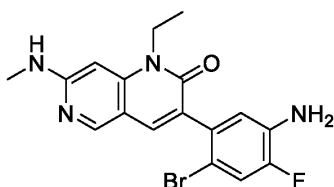


Formula (II)

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based on the weight of the compound of Formula (I).

23. The pharmaceutically acceptable composition of any one of claims 1-22, comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (II):

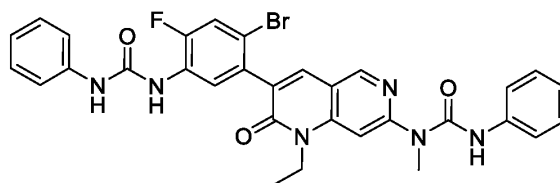


Formula (II)

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based on the weight of the compound of Formula (I).

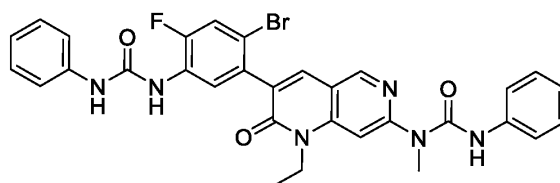
24. The pharmaceutically acceptable composition of any one of claims 1-23, comprising less than about 10 % by weight of a compound represented by Formula (III):



Formula (III)

5 based on the weight of the compound of Formula (I).

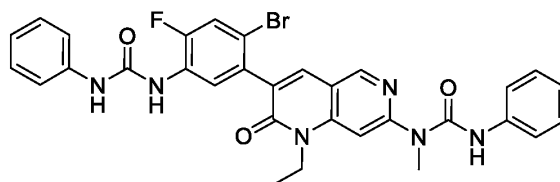
25. The pharmaceutically acceptable composition of any one of claims 1-24, comprising less than about 3 % by weight of a compound represented by Formula (III):



Formula (III)

10 based on the weight of the compound of Formula (I).

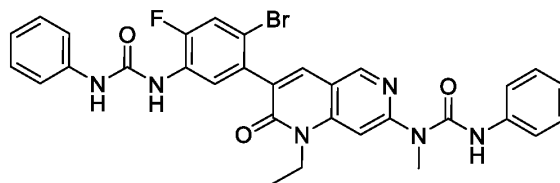
26. The pharmaceutically acceptable composition of any one of claims 1-25, comprising less than about 1 % by weight of a compound represented by Formula (III):



Formula (III)

15 based on the weight of the compound of Formula (I).

27. The pharmaceutically acceptable composition of any one of claims 1-26, comprising about 0.1 % by weight to about 0.5% by weight of a compound represented by Formula (III):



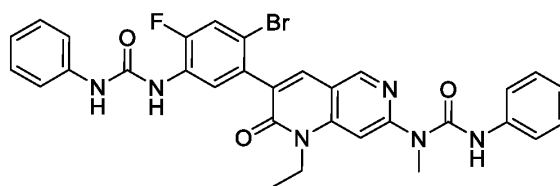
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Formula (III)

based on the weight of the compound of Formula (I).

28. The pharmaceutically acceptable composition of any one of claims 1-28, comprising about 0.01 % by weight to about 0.1% by weight of a compound represented by Formula (III):

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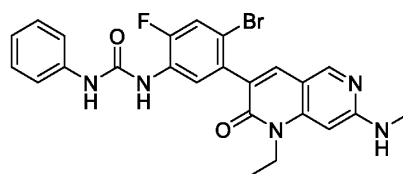


Formula (III)

based on the weight of the compound of Formula (I).

29. A pharmaceutically acceptable composition comprising a compound represented by Formula (I)

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Formula (I)

and a pharmaceutically acceptable excipient, wherein greater than about 96% by weight of the compound present in the pharmaceutically acceptable composition is in the amorphous form.

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30. The pharmaceutically acceptable composition of claim 29, wherein the amorphous form has a characteristic amorphous powder X-ray diffraction halo pattern.

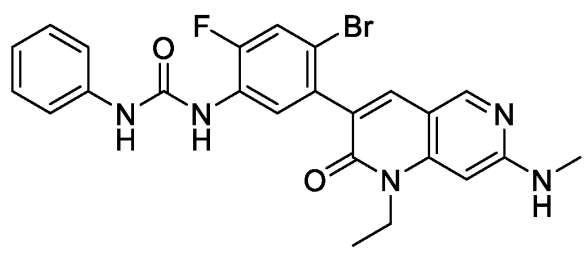
31 The pharmaceutically acceptable composition of claim 29 or 30 of any one of claims 1-3, where the amorphous form has a powder X-ray diffraction pattern substantially as shown
5 in Figure 1.

32. The pharmaceutically acceptable composition of claim 29 or 30, wherein the powder X-ray diffraction spectrum is obtained using Cu K α radiation.

33. The pharmaceutically acceptable composition of any one of claims 29-32, wherein the amorphous form of the compound has a glass transition temperature of about 125 °C.

10 34. The pharmaceutically acceptable composition of any one of claims 29-33, wherein the composition has no detectable amounts of any crystalline form of the compound of Formula (I).

35. A pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):



15

Formula (I)

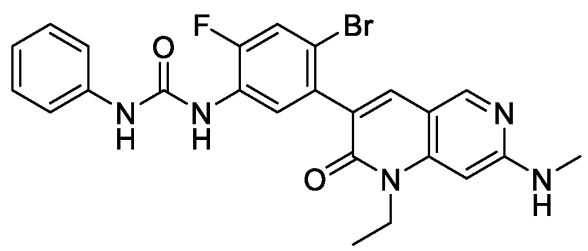
comprising:

an intragranular blend, wherein the intragranular blend comprises:

20 a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, hydroxypropyl methyl cellulose acetate succinate; a bulking agent and/or filler; and a lubricant and/or a glidant; and

an extragranular blend comprising a glidant and/or a lubricant.

36. A pharmaceutically acceptable composition for orally delivering to a patient 50 mg of a compound represented by Formula (I):



Formula (I)

5 comprising:

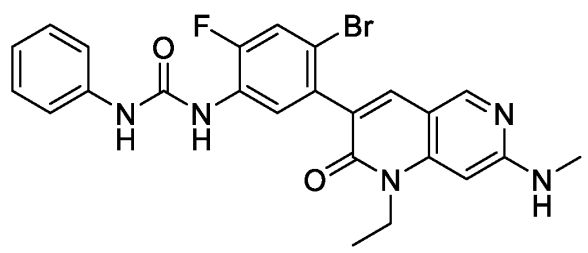
a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate;

a bulking agent,

a filler, and

10 a lubricant and/or a glidant.

37. A pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):



Formula (I)

15 comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

20 about 25-35% by weight of a bulking agent based on the total amount of the pharmaceutical composition;

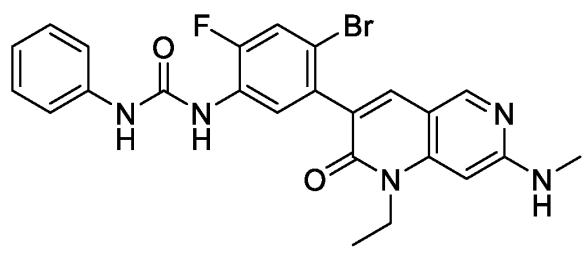
about 25-35% by weight of a filler based on the total amount of the pharmaceutical composition; and

an extragranular blend comprising a glidant and/or a lubricant.

38. The pharmaceutically acceptable tablet of claim 37, wherein the bulking agent is microcrystalline cellulose.

39. The pharmaceutically acceptable tablet of claim 37 or 38, wherein the filler is lactose or a hydrate thereof.

5 40. A pharmaceutically acceptable tablet having 50 mg of a compound represented by Formula (I):



Formula (I)

wherein the tablet comprises:

10 a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form, and hydroxypropyl methyl cellulose acetate succinate;

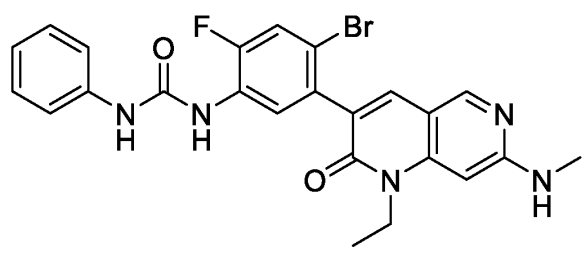
about 25-35% by weight microcrystalline cellulose based on the total weight of the tablet; and

about 25-35% by weight of lactose or a hydrate thereof based on the total
15 amount of the pharmaceutical composition.

41. The pharmaceutically acceptable tablet of claim 40, further comprising at least one of: magnesium stearate, crospovidone and silicon dioxide.

42. The pharmaceutically acceptable tablet of any one of claims 40 or 41, wherein the tablet disintegrates in less than 1 minute as tested using USP <701> for uncoated tablets.

43. A pharmaceutically acceptable composition for orally delivering 50 mg of a compound represented by Formula (I):



Formula (I)

5 comprising:

an intragranular blend, wherein the intragranular blend comprises:

a solid dispersion having 50 mg of the compound wherein the compound is present in amorphous form and hydroxypropyl methyl cellulose acetate succinate;

10 about 25-35% by weight microcrystalline cellulose based on the total amount of the pharmaceutical composition;

about 25-35%% by weight of lactose or a hydrate thereof based on the total amount of the pharmaceutical composition;

15 about 5% by weight of crospovidone based on the total amount of the of the pharmaceutical composition;

about 0.5% by weight of silicon dioxide based on the total amount of the of the pharmaceutical composition; and

about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition; and

20 an extragranular blend comprising about 0.5% by weight of silicon dioxide based on the total amount of the pharmaceutical composition; and (ii) about 0.5% by weight of magnesium stearate based on the total amount of the of the pharmaceutical composition.

44. The pharmaceutically acceptable composition or tablet of any one of claims 1-43, wherein the composition or tablet releases at least 80% of the compound after 10 minutes to 25 40 minutes when the composition is tested in 900 mL sodium acetate buffer at pH 4.5 using a USP Apparatus II (Paddle Method) at 37 °C, with a paddle speed of 75 rpm.

45. The pharmaceutically acceptable composition or tablet of any one of claims 1-44, wherein the composition or tablet releases at least 80% of the compound after 20 minutes when the composition is tested in 900 mL sodium acetate buffer at pH 4.5 using a USP Apparatus II (Paddle Method) at 37 °C, with a paddle speed of 75 rpm.
- 5 46. A method of treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), NF-1-deficient gastrointestinal stromal tumors, succinate dehydrogenase (SDH)-deficient gastrointestinal stromal tumors, KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell
10 leukemia, lung adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer in a patient in need thereof, comprising
15 administering to the patient a therapeutically effective amount of the composition or one or more of the tablets of claims 1-42.
47. A method of treating a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral
20 nerve sheath sarcoma, and hypereosinophilic syndrome in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the composition or one or more of the tablets of claims 1-45.
48. A method of treating a disease selected from the group consisting of KIT driven germ cell tumor (e.g., testicular germ cell), KIT driven skin cancer, or KIT driven renal cell
25 carcinoma in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the composition or one or more of the tablets of claims 1-45.
49. A method of treating a disease selected from the group consisting of penile cancer, PDGFRA driven penile cancer, prostate cancer, PDGFRA driven prostate cancer, PDGFRA
30 driven non-melanoma skin cancer, PDGFRA driven glioma, PDGFRA driven sarcoma, PDGFRA driven glioblastoma, or PDGFRA driven pancreatic cancer in a patient in need

thereof, comprising administering to the patient a therapeutically effective amount of the composition or one or more of the tablets of claims 1-45.

50. A method of treating a disease selected from the group consisting of vaginal cancer, prostate cancer, penile cancer, non-melanoma skin cancer, melanoma, or breast sarcoma in a
5 patient in need thereof, comprising administering to the patient a therapeutically effective amount of the composition or one or more of the tablets of claims 1-45, wherein the disease comprises a PDGFRAB mutation.

51. The method of claim 46, wherein the disease is gastrointestinal stromal tumors (GIST).

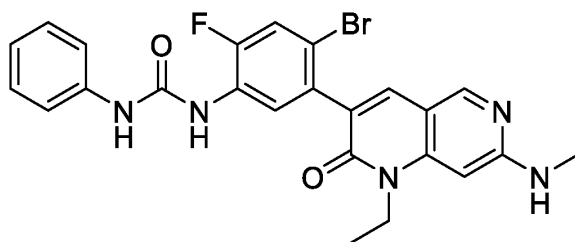
10 52. The use of the composition or tablets according to any one of claims 1-45 for the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, germ cell tumors of the seminoma or dysgerminoma, mastocytosis, mast cell leukemia, lung
15 adenocarcinoma, squamous cell lung cancer, glioblastoma, glioma, pediatric glioma, astrocytomas, sarcomas, malignant peripheral nerve sheath sarcoma, intimal sarcomas, hypereosinophilic syndrome, idiopathic hypereosinophilic syndrome, chronic eosinophilic leukemia, eosinophilia-associated acute myeloid leukemia, lymphoblastic T-cell lymphoma, and non-small cell lung cancer.

20 53. The use of a composition according to claim 52, for the preparation of a medicament for the treatment of a disease selected from the group consisting of gastrointestinal stromal tumors (GIST), KIT driven gastrointestinal stromal tumors, PDGFRA driven gastrointestinal stromal tumors, lung cancer, glioblastoma, a glioma, malignant peripheral nerve sheath sarcoma, and hypereosinophilic syndrome.

25 54. The use of claim 49, wherein the disease is gastrointestinal stromal tumors (GIST).

55. The method or use of any one of claims 46-54, wherein the disease is caused by the kinase activity of: c-KIT and/or PDGFRA, and/or oncogenic forms thereof.

56. A process for the preparation of the solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

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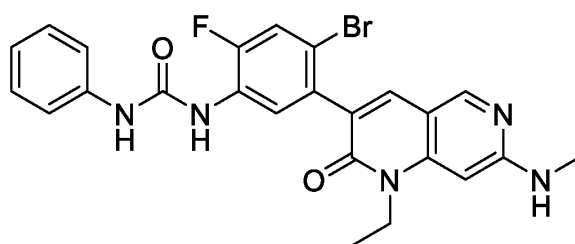
according to any one of claims 1-37, the process comprising:

- (a) mixing the compound of Formula (I), a solvent, the polymer and water to obtain a suspension;
- (b) optionally agitating and/or mixing the suspension while maintaining a temperature of about 10 to about 25 °C;
- (c) heating the suspension to dissolve the suspended particles prior to introduction into a spray-dryer; and
- (d) spray-drying the suspension to obtain a spray-dried dispersion;
- (e) drying the spray-dried dispersion; thereby obtaining the solid dispersion.

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57. The process of claim 56, wherein heating comprises passing the suspension through an in-line heat exchanger.

58. A solid dispersion comprising an amorphous form of a compound of Formula (I)



Formula (I)

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produced by the process of claim 55 or 56.