to the development of secondary mutations in KIT. Secondary resistance mutations usually arise in the catalytic domain of the kinase: 1) at the switch pocket, which typically occur in KIT exons 13 and 14 or PDGFRA exons 14 and 15 and sterically disrupt drug binding or conformationally activate KIT, and 2) in the activation loop switch encoded by KIT exons 17 and 18 and PDGFRA 18. Activation loop mutations act by shifting the kinase into an activated Type I or on-state conformation that is less amenable to drug binding by any of the approved Type II TKIs. Although uncommon in primary GIST (1%-2% of newly diagnosed cases), mutations in exons 13, 14 and 17 are often responsible for acquired imatinib resistance, with exon 17 mutations alone accounting for as many as 50% of the acquired resistance cases to imatinib, and later to sunitinib. A need exists for a TKI that can broadly inhibit clinically relevant KIT and PDGFRA mutations.

## SUMMARY

**[0006a]** In a first aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 300 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[0006b]** In another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 600 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[0006c]** In yet another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 100 mg to 250 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

**[0006d]** In a further aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising ripretinib is to be orally administered

to the patient daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[0006e]** In another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein one or more tablets comprising ripretinib is to be orally administered to the patient, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

**[0006f]** In yet another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of ripretinib is to be orally administered to the patient once daily, and wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib.

**[0006g]** In a further aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg ripretinib is to be orally administered daily to the patient, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

**[0006h]** In another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein 150 mg of ripretinib is to be orally administered to the patient once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[0006i]** In yet another aspect, the present disclosure refers to a use of ripretinib in the manufacture of a medicament for treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, wherein 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, is to be orally administered to the patient once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient is to be provided as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

the patient is to be monitored more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

**[0007]** Described herein are methods of treating a gastrointestinal stromal tumor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of ripretinib or a pharmaceutically acceptable salt thereof.

**[0008]** For example, in one ~~embodiment~~example described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 300 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[0009]** For example, in one ~~embodiment~~example described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[00010]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[00011]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to

100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib. In some examples, the tablets comprise 50 mg of ripretinib. In some ~~embodiment~~examples, the tablets comprise 75 mg of ripretinib. In some ~~embodiment~~examples, the tablets comprise 100 mg of ripretinib.

**[00012]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient one or more tablets comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib, a previous second line administration of sunitinib, and a previous third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some ~~embodiment~~examples, the tablets comprise 50 mg of ripretinib. In some example, the tablets comprise 75 mg of ripretinib. In some example, the tablets comprise 100 mg of ripretinib. In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 250 mg of ripretinib daily, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

**[00013]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

**[00014]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or

wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib. In some ~~embodiment~~example, the tablets comprise 50 mg of ripretinib. In some ~~embodiment~~example, the tablets comprise 75 mg of ripretinib. In some ~~embodiment~~example, the tablets comprise 100 mg of ripretinib.

**[00015]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, e.g., 100 mg to 250 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 250 mg, e.g., 150 mg, e.g., 300 mg, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

**[00016]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.

**[00017]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib. In some ~~embodiment~~example, the tablets comprise 50 mg of ripretinib. In some ~~embodiment~~example, the tablets comprise 75 mg of ripretinib. In some ~~embodiment~~example, the tablets comprise 100 mg of ripretinib.

**[00018]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib. In some ~~embodiment~~examples, after at least 4 weeks of the daily ripretinib administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1. In some ~~embodiment~~examples, orally administering to the patient 150 mg of ripretinib once daily comprises administering to the patient three tablets each tablet comprising 50 mg of ripretinib. In some ~~embodiment~~examples, one of the three or more kinase inhibitors is imatinib. In some ~~embodiment~~examples, the patient was previously administered imatinib, sunitinib and regorafenib.

**[00019]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg daily ripretinib, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

**[00020]** In another ~~embodiment~~example, described herein is a method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

**[00021]** In another ~~embodiment~~example, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150 200, or 300 mg of ripretinib daily or twice daily for at least 28 days.

**[00022]** In another ~~embodiment~~example, described herein is a method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150, or 200 mg of ripretinib daily or twice daily for at least 28 days.

**[00023]** In another ~~embodiment~~example, descried herein is a method of treating a patient suffering from Grade 3 palmer-plantar erythrodysesthia syndrome while being administered 150 mg ripretinib daily or twice daily, comprising withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantarplantar erythrodysesthia syndrome, then administering to the patient 100 mg daily (e.g., 100 mg once daily) ripretinib for at least 28 days.

**[00024]** In another ~~embodiment~~example, descried herein is a method of treating a patient suffering from Grade 2 palmer-plantarplantar erythrodysesthia syndrome upon administration of 150 mg ripretinib daily or twice daily, comprising a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily

ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.

**[00025]** In another ~~embodiment~~example, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, provides an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and monitoring the patient more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

**[00026]** In another ~~embodiment~~example, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a proton pump inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein administration of the ripretinib and proton pump inhibitor to the patient provides no clinically significant difference in the plasma exposure of ripretinib in the patient as compared to administration of ripretinib without concurrent treatment of the proton pump inhibitor.

**[00027]** In another ~~embodiment~~example, described herein is a method of treating a gastrointestinal stromal tumor in a patient in need thereof, the method comprising orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, wherein the ripretinib is administered to the patient with food or without food.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[00028]** **FIG. 1** depicts a plot of survival probability with respect to progression-free survival (PFS) for patients on ripretinib and patients on placebo as described in Example 2.

**[00029]** **FIG. 2** depicts a plot of survival probability with respect to overall survival (OS) for patients on ripretinib and patients on placebo as described in Example 2.

## CLAIMS

What is claimed is:

1. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein ~~comprising orally administering to the patient~~ 100 mg to 300 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

2. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein ~~comprising orally administering to the patient~~ 100 mg to 600 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

3. The ~~method~~ use of claim 1 or 2, wherein the patient is to be administered 150 mg of ripretinib daily.

~~4. The method of claim 2, wherein the patient is administered 500 mg of ripretinib daily.~~

4~~5~~. The ~~method~~ use of claim 1 or 2, wherein the patient is to be administered 150 mg of ripretinib once daily.

5~~6~~. The ~~method~~ use of claim 2, wherein the patient is to be administered 150 mg of ripretinib twice daily.

~~7. The method of claim 2, wherein the patient is administered 250 mg of ripretinib twice daily.~~

~~8. The method of any one of claims 1-7, wherein the patient was only previously treated with the first line administration of imatinib.~~

~~9. The method of claim 8, wherein the patient was not previously given a second line administration of sunitinib therapy and/or a third-line administration of regorafenib therapy.~~

~~10. The method of any one of claims 1-9, wherein the patient has a non-nodal tumor lesion greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.~~

~~11. The method of any one of claims 1-10, wherein administering ripretinib is a 42-day cycle comprising daily administration of ripretinib without administering sunitinib.~~

~~12. The method of claim 11, wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1.~~

~~13. The method of claim 11 or 12, wherein the patient has a significant progression free survival as compared to a second-line daily administration of 50 mg sunitinib for four weeks followed by two weeks without daily administrations on a 42-day cycle, wherein the patient's tumor has progressed from, or the patient was intolerant to, the previous first line administration of imatinib.~~

6~~14~~. The ~~method~~ use of any one of claims 1-5~~13~~, wherein the tumor has, a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation, or a PDGFRA exon 18 activation loop mutation.

~~15. The method of claim 14, wherein the mutation is a PDGFRA D842V mutation.~~

~~16. The method of any one of claims 1-15, wherein the tumor has an imatinib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation, and a PDGFRA exon 18 activation loop mutation.~~

~~17. The method of claim 16, wherein the imatinib resistant mutation is a PDGFRA D842V mutation.~~

~~18. The method of claim 16 or 17, wherein the tumor has an imatinib resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.~~

~~19. The method of any one of claims 15-18, wherein the tumor has an imatinib resistant KIT exon 17 mutation.~~

7~~20~~. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, wherein ~~comprising orally administering to the patient~~ 100 mg to 250 mg of ripretinib is to be orally administered to the patient daily, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

~~21. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib, or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.~~

2~~28~~. The ~~method~~ use of claim ~~20 or 21~~7, wherein the patient is to be administered 150 mg of ripretinib daily.

~~23. The method of claim 21, wherein the patient is administered 500 mg of ripretinib daily.~~

9~~24~~. The ~~method~~ use of claim ~~20 or 21~~7, wherein the patient is to be administered 150 mg of ripretinib once daily.

~~25. The method of claim 21, wherein the patient is administered 150 mg of ripretinib twice daily.~~

~~26. The method of claim 21, wherein the patient is administered 250 mg of ripretinib twice daily.~~

~~27. The method of any one of claims 20-26, wherein the patient has at least one measurable tumor lesion according to modified RECIST Version 1.1 within 21 days prior to the first dose of ripretinib.~~

~~28. The method of any one of claims 20-27, wherein the patient has a non-nodal tumor lesion of greater than or equal to 1.0 cm in the long axis or greater than or equal to double the slide thickness in the long axis, within 21 days prior to the first dose of ripretinib.~~

~~29. The method of any one of claims 20-28, wherein the tumor has, a KIT exon 9 mutation, a PDGFRA exon 18 mutation, a PDGFRA exon 12 mutation or a PDGFRA exon 18 activation loop mutation.~~

~~30. The method of claim 29, wherein the mutation is a PDGFRA D842V mutation.~~

~~31. The method of any one of claims 20-30, wherein the tumor has an imatinib resistant, sunitinib resistant, and/or regorafenib resistant mutation selected from the group consisting of a KIT exon 17 activation loop mutation, a KIT exon 18 activation loop mutation, a KIT exon 13 mutation, a KIT exon 14 mutation, a KIT exon 18 mutation, a PDGFRA exon 12 mutation, a PDGFRA exon 14 mutation, a PDGRFA exon 15 mutation and a PDGFRA exon 18 activation loop mutation.~~

~~32. The method of claim 31, wherein the resistant mutation is a PDGFRA D842V mutation.~~

~~33. The method of claim 31 or 32, wherein the tumor has a drug resistant mutation selected from the group consisting of KIT exon 13 or 14 mutation, PDGFRA exon 14 or 15 mutation, a KIT 17 or 18 activation loop mutation, and a PDGFRA 18 activation loop mutation.~~

~~34. The method of any one of claims 20-33, wherein the tumor has a drug resistant KIT exon 17 mutation.~~

~~35. The method of any one of claims 20-34, wherein administering ripretinib is a 42-day cycle comprising daily administration of ripretinib without administering sunitinib.~~

~~36. The method of claim 35, wherein, after at least one 42-day cycle, the patient has a progression-free survival as measured using mRECIST v1.1.~~

~~37. The method of any one of claims 20-36, wherein the patient has at least a 5 or 6 month progression-free survival as compared to placebo after at least 4 weeks of daily administration of ripretinib.~~

10~~38~~. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, ~~comprising orally administering to the patient~~ wherein one or more tablets comprising ripretinib is to be orally administered to the patient daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

11~~39~~. The ~~method~~ use of claim 10~~38~~, wherein the patient is to be administered three tablets each comprising 50 mg of ripretinib once daily.

~~40. The method of claim 38, wherein the patient is administered two tablets each comprising 50 mg of ripretinib once daily.~~

~~41. The method of claim 38, wherein the patient is administered one tablet comprising 50 mg of ripretinib once daily.~~

12~~42~~. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, ~~comprising orally administering to the patient to the patient~~ wherein one or more tablets comprising ripretinib is to be orally administered to the patient, and wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib or wherein the patient has a documented intolerance to one or more of imatinib, sunitinib and/or regorafenib.

13~~43~~. The ~~method~~ use of claim 12~~42~~, wherein the patient is to be administered, once daily, three tablets each comprising 50 mg of ripretinib.

~~44. The method of claim 42, wherein the patient is administered, once daily two tablets each comprising 50 mg of ripretinib.~~

~~45. The method of claim 42, wherein the patient is administered one tablet comprising 50 mg of ripretinib once daily.~~

~~46. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100 mg to 600 mg of ripretinib daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.~~

~~47. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 150 mg of ripretinib once daily, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.~~

~~48. A method of treating a patient suffering from an advanced gastrointestinal stromal tumor, comprising orally administering to the patient, on a daily basis, one or more tablets each comprising ripretinib, e.g., tablets each comprising 50 mg to 100 mg of ripretinib, wherein the patient was previously administered at least two tyrosine kinase inhibitors before administration of the ripretinib.~~

~~49. The method of claim 48, wherein the patient is administered, once daily, three tablets each comprising 50 mg of ripretinib.~~

~~50. The method of any one of claims 46-49, wherein the patient has previously been administered two separate tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.~~

14~~51~~. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, ~~comprising orally administering to the patient~~wherein 150 mg of ripretinib is to be orally administered to the patient once daily, and wherein the patient was previously administered three or more kinase inhibitors before administration of the ripretinib.

~~52. The method of claim 51, wherein after at least 4 weeks of the daily ripretinib administration, the patient has at least a 5-month progression-free survival as measured using mRECIST v1.1.~~

~~53. The method of claim 51 or 52, wherein orally administering to the patient 150 mg of ripretinib once daily comprises administering to the patient three tablets each tablet comprising 50 mg of ripretinib.~~

~~54. The method of any one of claims 51-53, wherein one of the three or more kinase inhibitors is imatinib.~~

1555. The ~~method~~ use of claim 14 ~~any one of claims 51-54~~, wherein the patient was previously administered imatinib, sunitinib and regorafenib.

1656. The ~~method~~ use of ~~any one of claims 51-55~~claim 14 or 15, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the method further comprises~~ a) ~~withholding~~ administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then ~~administering to the patient~~ 100 mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

1757. The ~~method~~ use of claim 14 or 15~~any one of claims 51-55~~, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the method further comprises:~~ a) ~~withholding~~ administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythroor~~or~~ysesthesia syndrome within 7 days of withholding administration, then ~~administering to the patient~~ 150 mg ~~daily~~ ripretinib is to be administered daily to the patient; or c) if the patient has not recovered, then ~~administering to the patient~~ 100mg ~~daily~~ ripretinib is to be administered daily to the patient~~-~~ for at least 28 days.

1858. Use of ripretinib in the manufacture of a medicament for~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, ~~comprising orally administering to the patient~~ wherein 150 mg ~~daily~~ ripretinib is to be orally administered daily to the patient, wherein the patient's tumor has progressed from, or the patient was intolerant to, a first line administration of imatinib, a second line administration of sunitinib, and a third line administration of regorafenib.

1959. The ~~method~~ use of claim 1858, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the method further comprises~~ a) ~~withholding~~ administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then ~~administering to the patient~~ 100 mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

2060. The ~~method~~ use of claim 1858, wherein if the patient suffers from a Grade 2 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the~~

~~method further comprises:~~ a) ~~withholding~~ administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythrod~~or~~ysesthesia syndrome within 7 days of withholding administration, then ~~administering to the patient~~ 150 mg ~~daily~~ ripretinib is to be administered to the patient daily; or c) if the patient has not recovered, then ~~administering to the patient~~ 100mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

21~~61~~. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a patient suffering from an advanced gastrointestinal stromal tumor, ~~comprising orally administering to the patient~~ wherein 150 mg of ripretinib is to be orally administered to the patient once or twice daily, wherein the patient's tumor has progressed from, or the patient was intolerant to, a previous first line administration of imatinib.

22~~62~~. The ~~method~~ use of claim 21~~61~~, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the method further comprises~~ a) ~~withholding~~ administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then ~~administering to the patient~~ 100 mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

23~~63~~. The ~~method~~ use of any one of claims 3-7~~20~~, wherein if the patient suffers from Grade 3 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the method further comprises~~ a) ~~withholding~~ administration of ripretinib is to be withheld for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome, then ~~administering to the patient~~ 100 mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

24~~64~~. The ~~method~~ use of any one of claims 3-7~~20~~, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthesia syndrome upon administration of the ripretinib, ~~the method further comprises:~~ a) ~~withholding~~ administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthesia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythro~~or~~ysesthesia syndrome within 7 days of withholding administration, then ~~administering to the patient~~ 150 mg ~~daily~~ ripretinib is to be administered to the patient daily; or c) if the patient has not recovered, then

~~administering to the patient~~ 100mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

25~~65~~. The ~~method~~ use of any one of claims 3-7~~20~~, ~~-~~wherein if the patient suffers from a Grade 3 adverse disorder selected from arthralgia or myalgia upon administration of the ripretinib, ~~the method further comprises:~~ a) ~~withholding~~ administration of ripretinib is to be withheld until the patient has less than or equal to Grade 1 adverse disorder, then ~~administering to the patient~~ 100 mg ~~daily~~ ripretinib is to be administered to the patient daily for at least 28 days.

26~~66~~. The ~~method~~ use of any one of claims 3-7~~20~~, ~~-~~wherein if the patient suffers from Grade 3 hypertension upon administration of the ripretinib, ~~the method further comprises withholding~~ administration of ripretinib is to be withheld until the patient's blood pressure is controlled, and if the patient has less than or equal to Grade 1 blood pressure is, ~~administering to the patient~~ 150 mg ~~daily~~ ripretinib is to be administered to the patient daily, or if the patient has more than Grade 1 blood pressure, ~~administering~~ 100 mg ~~daily~~ ripretinib is to be administered to the patient daily.

~~67. A method for achieving at least 5 months of progression free survival as determined by mRECIST 1.1 in a patient having an advanced gastrointestinal stromal tumor, comprising orally administering to the patient 100, 150, 200, or 300 mg of ripretinib daily or twice daily for at least 28 days.~~

~~68. The method of claim 67, wherein the patient has been administered at least one previous kinase inhibitor.~~

~~69. The method of claim 67-68, wherein the patient has been administered at least three previous kinase inhibitors.~~

~~70. The method of claim 68 or 69, wherein the at least one previous kinase inhibitor is imatinib.~~

~~71. The method of any one of claims 67-70, comprising orally administering to the patient 100, 150 or 200 mg of ripretinib daily or twice daily for at least 4 months.~~

~~72. A method of treating a patient suffering from Grade 3 palmer-plantar erythrodysesthia syndrome while being administered 150 mg ripretinib daily or twice daily,~~

~~comprising withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.~~

~~73. A method of treating a patient suffering from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of 150 mg ripretinib daily or twice daily, comprising a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.~~

2774. Use of ripretinib in the manufacture of a medicament for ~~A method of~~ treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a CYP3A4 inhibitor, ~~the method comprising:~~wherein

~~orally administering to the patient~~ 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, is to be orally administered to the patient once or twice daily, and wherein upon administration of the ripretinib and the CYP3A4 inhibitor, ~~provides~~ an increased ripretinib area under the plasma concentration curve ($AUC_{0\text{-}inf}$) of 80% or more in the patient is to be provided as compared to administration of ripretinib without concurrent treatment of the CYP3A4 inhibitor, and therefore the patient is at higher risk of an adverse event; and

~~monitoring~~ the patient is to be monitored more frequently, as compared to a patient not being treated with a CYP3A4 inhibitor, for the adverse event.

~~75. The method of claim 74, wherein if the patient suffers from a Grade 3 palmer-plantar erythrodysesthia syndrome adverse event, the method further comprises a) withholding administration of ripretinib for at least 7 days or until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome, then administering to the patient 100 mg daily ripretinib for at least 28 days.~~

~~76. The method of claim 75, wherein if the patient suffers from Grade 2 palmer-plantar erythrodysesthia syndrome upon administration of the ripretinib, the method further~~

~~comprises: a) withholding administration of ripretinib until the patient has less than or equal to Grade 1 palmer-plantar erythrodysesthia syndrome or baseline; b) if the patient recovers from the palmer-plantar erythorysesthia syndrome within 7 days of withholding administration, then administering to the patient 150 mg daily ripretinib or c) if the patient has not recovered, then administering to the patient 100mg daily ripretinib for at least 28 days.~~

~~77. The method of any one of claims 74-76, wherein the CYP3A4 inhibitor is selected from the group consisting of itraconazole, ketoconazole, clarithromycin, and indinavir.~~

~~78. The method of any one of claims 74-77, wherein the CYP3A4 inhibitor is itraconazole.~~

~~79. The method of any one of claims 74-78, wherein the patient has previously been administered one or more tyrosine kinase inhibitors, each selected from the group consisting of imatinib, sunitinib, regorafenib, lapatinib, gefitinib, erlotinib, vatalanib, crenolanib, and pharmaceutically acceptable salts thereof.~~

~~80. A method of treating a gastrointestinal stromal tumor in a patient in need thereof, wherein the patient is being treated concurrently with a proton pump inhibitor, the method comprising: orally administering to the patient 100 mg or 150 mg of ripretinib, or a pharmaceutically acceptable salt thereof, once or twice daily, and wherein upon administration of the ripretinib and proton pump inhibitor, provides no clinically significant difference in the plasma exposure of ripretinib in the patient as compared to administration of ripretinib without concurrent treatment of the proton pump inhibitor.~~

~~81. The method of claim 80, wherein the proton pump inhibitor is selected from the group consisting of pantoprazole, omeprazole, lansoprazole, rabeprazole, esomeprazole, and dexlansoprazole.~~

~~82. The method of claim 80 or 81, wherein the proton pump inhibitor is pantoprazole.~~

~~83. The method of any one of claims 80-82, wherein the patient is being treated concurrently with 40 mg of the proton pump inhibitor once daily.~~

~~84. A method of treating a gastrointestinal stromal tumor in a patient in need thereof, the method comprising orally administering to the patient 100 mg or 150 mg of ripretinib, or~~

~~a pharmaceutically acceptable salt thereof, once or twice daily, wherein the ripretinib is administered to the patient with food or without food.~~

~~85. The method of claim 83, wherein the food comprises a high-fat meal.~~