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(54) Title: PHARMACEUTICAL COMPOSITIONS AND USE THEREOF

(57) Abstract: The present disclosure provides pharmaceutical compositions comprising micronized Compound A and methods for treating diseases using the pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS AND USE THEREOF

[001] Angiogenesis is a process wherein new blood vessels can grow from existing vasculature. That process can occur in wound healing of the body, such as the restoration of blood flow in tissue injury, for example, an injury of the hand. Excess angiogenesis, however, might be initiated under specific pathological conditions, for example tumor, AMD (age-related macular degeneration), rheumatoid arthritis, psoriasis, etc. Under such circumstances, new blood vessels may undesirably tend to provide pathological tissues with nutrition and injure the normal tissues. For example, cancer cells may enter into blood circulation through new blood vessels and invade normal tissues.

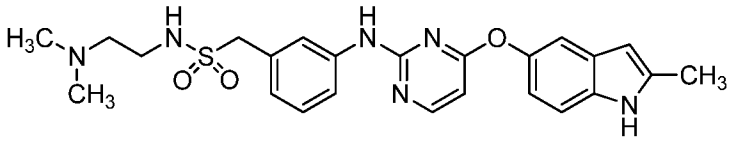
[002] VEGF (Vascular Endothelial Growth Factor) and its receptor VEGFR-2 (also called KDR, kinase insert domain-containing receptor) can form the major pathway for the formation of new blood vessels. It has been indicated that inhibition of KDR can cause apoptosis of endothelial cells, which consequently block the angiogenesis process (Rubin M. Tuder, Chest, 2000; 117:281). Thus, KDR inhibitors can be used for the treatment of angiogenesis- related diseases.

[003] FGF (Fibroblast Growth Factor) is a pro-angiogenesis molecule as is VEGF. During angiogenesis, VEGF is thought to be critical in the neovascularization process. The FGF (Fibroblast Growth Factor)/FGFR (Fibroblast Growth Factor Receptor) axis plays roles in functionally maturing newly formed vessels. In addition, aberrant activation of FGF family members and their cognate receptors have been found in multiple cancers, such as breast, bladder and prostate cancers. FGFR1 and its binding partners FGF1, FGF2,

FGF8b and FGF17 are also elevated. In other tumor types, FGFR1 is implicated as an oncogene whose expression is increased compared with normal tissue. Therefore, blockade of FGF/FGFR signaling may be beneficial for treatment of cancers associated with FGF/FGFR activation.

[004] Neuroendocrine tumors (NET) is a rare cancer of the hormone system, normally slow growth. NET affects the gastrointestinal tract, lung, pancreas, and several other organs.

[005] The compound of Formula A ("Compound A" and "compound of formula A" are used interchangeably herein)), e.g., *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-of yl)amino)phenyl)-methanesulfonamide, and/or a pharmaceutically acceptable salt thereof was disclosed in US Patent Application No.: 13/510,249 (the '249 application), which is a national stage of PCT/CN2010/078997, filed November 23, 2010, now issued as U.S. Patent No.: 8,658,658 (the '658 patent). The '658 patent is incorporated herein by reference in its entirety.



Formula A

N-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)-methanesulfonamide

[006] Solid-state crystalline forms I and II of the compound of Formula A, i.e., Form I *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)-methanesulfonamide and Form II *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-

yl)amino)phenyl)-methanesulfonamide, and methods of preparation thereof had been discovered and were disclosed in the '658 patent.

[007] Disclosed herein is a method of treating a subject in recognized need of treatment for NET, comprising administering to said subject in need thereof an effective amount of the compound of Formula A and/or a pharmaceutically acceptable salt thereof. In some embodiments, the compound of Formula A is Form I. In some embodiments, the compound of Formula A is substantially pure Form I. In some embodiments, the compound of Formula A is Form II. In some embodiments, the compound of Formula A is substantially pure Form II. In some embodiments, the compound of Formula A and/or a pharmaceutically acceptable salt thereof are micronized with a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments, Form I, substantially pure Form I, Form II, or substantially pure Form II is micronized with a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments, the D90 value ranges from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments, the D90 value ranges from 2.0 to 5.0 μm, for example, the D90 value is 3.0, 3.5, or 4.0 μm. In some embodiments, the D90 value ranges from 9.0 to 12.0 μm, for example, the D90 value is 9.5 or 10.0 μm.

[008] Also disclosed is a method of treating a subject in recognized need of treatment for NET, comprising administering to said subject in need thereof an effective amount of a pharmaceutical composition comprising

at least one pharmaceutically acceptable carrier, and

at least one active ingredient chosen from Compound A and pharmaceutically acceptable salts thereof. In some embodiments, the at least one active ingredient is Compound A. In some embodiments, Compound A is Form I. In some embodiments, Compound A is substantially pure Form I. In some embodiments, Compound A is Form II. In some embodiments, Compound A is substantially pure Form II. In some embodiments, Form I, substantially pure Form I, Form II, or substantially pure Form II is micronized with a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments, the D90 value ranges from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments, the D90 value ranges from 2.0 to 5.0 μm, for example, the D90 value is 3.0, 3.5, or 4.0 μm. In some embodiments, the D90 value ranges from 9.0 to 12.0 μm, for example, the D90 value is 9.5 or 10.0 μm.

[009] Also disclosed herein is a first pharmaceutical composition, comprising

micronized Compound A , and/or

micronized at least one pharmaceutically acceptable salt of Compound A, and

at least one pharmaceutically acceptable carrier.

In some embodiments, the micronized Compound A and/or the micronized at least one pharmaceutically acceptable salt thereof has a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0

μm. In some embodiments, the D90 value ranges from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments, the D90 value ranges from 2.0 to 5.0 μm, for example, the D90 value is 3.0, 3.5, or 4.0 μm. In some embodiments, the D90 value ranges from 9.0 to 12.0 μm, for example, the the D90 value is 9.5 or 10.0 μm.

[010] In some embodiments of the first pharmaceutical composition, the micronized Compound A is Form I. In some embodiments of the first pharmaceutical composition, the micronized Compound A is substantially pure Form I.

[011] In some embodiments of the first pharmaceutical composition, the micronized Compound A is Form II. In some embodiments of the first pharmaceutical composition, the micronized Compound A is substantially pure Form II.

[012] In some embodiments of the first pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments of the first pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments of the first pharmaceutical composition, the micronized Form I or

micronized substantially pure Form I has a D90 value ranging from 2.0 to 5.0 μm, for example, has a D90 value as 3.0, 3.5, or 4.0 μm. In some embodiments of the first pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 9.0 to 12.0 μm, for example, has a D90 value as 9.5 or 10.0 μm.

[013] In some embodiments of the first pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments of the first pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments of the first pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value ranging from 2.0 to 5.0 μm, for example, has a D90 value as 3.0, 3.5, or 4.0 μm. In some embodiments of the first pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value ranging from 9.0 to 12.0 μm, for example, has a D90 value as 9.5 or 10.0 μm.

[014] In some embodiments of the first pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from mannitol, microcrystalline cellulose, starch, lactose, dextrin, sorbitol, sodium starch glycolate, silicon dioxide, polyvinylpyrrolidone (PVP), and magnesium stearate. In some embodiments of the first pharmaceutical composition, the at least one

pharmaceutically acceptable carrier is chosen from mannitol, microcrystalline cellulous, sodium starch glycolate, silicon dioxide, and magnesium stearate. In some embodiments of the first pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from microcrystalline cellulous and magnesium stearate.

[015] In some embodiments of the first pharmaceutical composition, the micronized Compound A , such as micronized Form I/substantially pure Form I or micronized Form II/substantially pure Form II, and/or micronized at least one pharmaceutically acceptable salt thereof can be present in an amount of 1, 5,10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a tablet or capsule, such as in a capsule.

[016] Also disclosed herein is a second pharmaceutical composition, comprising

micronized Compound A , and

at least one pharmaceutically acceptable carrier.

In some embodiments, the particle size distribution (PSD) of the micronized Compound A has a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments, the D90 value ranges from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments, the D90 value ranges from 2.0 to 5.0 μm, for example, the D90 value is 3.0, 3.5, or 4.0 μm. In some embodiments, the D90 value ranges from 9.0 to 12.0 μm, for example, the D90 value is 9.5 or 10.0 μm.

[017] In some embodiments of the second pharmaceutical composition, the micronized Compound A is Form I. In some embodiments of the second pharmaceutical composition, the micronized Compound A is substantially pure Form I.

[018] In some embodiments of the second pharmaceutical composition, the micronized Compound A is Form II. In some embodiments of the second pharmaceutical composition, the micronized Compound A is substantially pure Form II.

[019] In some embodiments of the second pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments of the second pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments of the second pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 2.0 to 5.0 μm, for example, has a D90 value as 3.0, 3.5, or 4.0 μm. In some embodiments of the second pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 9.0 to 12.0 μm, for example, has a D90 value as 9.5 or 10.0 μm.

[020] In some embodiments of the second pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value has

a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments of the second pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments of the second pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value ranging from 2.0 to 5.0 μm, for example, has a D90 value as 3.0, 3.5, or 4.0 μm. In some embodiments of the second pharmaceutical composition, the micronized Form II or micronized substantially pure Form II has a D90 value ranging from 9.0 to 12.0 μm, for example, has a D90 value as 9.5 or 10.0 μm.

[021] In some embodiments of the second pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from mannitol, microcrystalline cellulous, starch, lactose, dextrin, sorbitol, sodium starch glycolate, silicon dioxide, polyvinylpyrrolidone (PVP), and magnesium stearate. In some embodiments of the second pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from mannitol, microcrystalline cellulous, sodium starch glycolate, polyvinylpyrrolidone (PVP), and magnesium stearate. In some embodiments of the second pharmaceutical composition, the at least one pharmaceutically acceptable carrier comprises microcrystalline cellulous, sodium starch glycolate, silicon dioxide, and magnesium stearate. In some embodiments of the second pharmaceutical composition, the at least one

pharmaceutically acceptable carrier comprises microcrystalline cellulous and magnesium stearate.

[022] In some embodiments of the second pharmaceutical composition, the micronized Compound A can be present in an amount of 1, 5,10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a tablet or capsule, such as in a capsule.

[023] Also disclosed herein is a third pharmaceutical composition comprising micronized Compound A that is Form I or substantially pure Form I , and

at least one pharmaceutically acceptable carrier.

[024] In some embodiments of the third pharmaceutical composition, the micronized Form I or substantially pure Form I has a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments of the third pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments of the third pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 2.0 to 5.0 μm, for example, has a D90 value as 3.0, 3.5, or 4.0 μm. In some embodiments of the third pharmaceutical composition, the micronized Form I or micronized substantially pure Form I has a D90 value ranging from 9.0 to 12.0 μm, for example, has a D90 value as 9.5 or 10.0 μm.

[025] In some embodiments of the third pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from mannitol, microcrystalline cellulous, starch, lactose, dextrin, sorbitol, sodium starch glycolate, silicon dioxide, polyvinylpyrrolidone (PVP), and magnesium stearate. In some embodiments of the third pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from mannitol, microcrystalline cellulous, sodium starch glycolate, polyvinylpyrrolidone (PVP), and magnesium stearate. In some embodiments of the third pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from microcrystalline cellulous, sodium starch glycolate, silicon dioxide, and magnesium stearate. In some embodiments of the third pharmaceutical composition, the at least one pharmaceutically acceptable carrier is chosen from microcrystalline cellulous and magnesium stearate.

[026] In some embodiments of the third pharmaceutical composition, the micronized Compound A that is Form I or substantially pure Form I can be present in an amount of 1, 5,10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a tablet or capsule, such as in a capsule.

[027] Also disclosed herein is a method of treating a subject in recognized need of treatment for neuroendocrine tumors (NET), comprising administering to said subject in need thereof an effective amount of the first pharmaceutical composition, including each of the embodiments thereof, as disclosed above.

[028] Also disclosed herein is a method of treating a subject in recognized need of treatment for neuroendocrine tumors (NET), comprising administering to

said subject in need thereof an effective amount of the second pharmaceutical composition, including each of the embodiments thereof, as described above.

[029] Also disclosed herein is a method of treating a subject in recognized need of treatment for neuroendocrine tumors (NET), comprising administering to said subject in need thereof an effective amount of the third pharmaceutical composition, including each of the embodiments thereof, as disclosed above.

[030] Also disclosed herein is a method of treating a subject in recognized need of treatment for at least one disease responsive to FGFR1 inhibition, such as cancer, and/or at least one disease responsive to KDR inhibition, such as angiogenesis-related disorders, comprising administering to said subject in need thereof an effective amount of a pharmaceutical composition selected from the first, second, and third pharmaceutical composition, including each of the embodiments thereof, as disclosed above. In some embodiments, angiogenesis-related disorders as described herein include but are not limited to cancer and age-related macular degeneration. In some embodiments, cancers as described herein include but are not limited to lung cancer, head and neck cancer, colorectal cancer, pancreatic cancer, colon cancer, breast cancer, ovarian cancer, prostate cancer, stomach cancer, kidney cancer, liver cancer, brain cancer, bone cancer, neuroendocrine tumors, sarcoma, such as soft tissue sarcoma, and leukemia.

[031] Also disclosed is a method of preparing a tablet or capsules, comprising:

mixing at least one active pharmaceutical ingredient chosen from Compound A, pharmaceutically acceptable salts thereof, and Forms I and II of

Compound A, with at least one pharmaceutically acceptable carrier, wherein Compound A, pharmaceutically acceptable salts thereof , and Forms I and II of the compound of Formula A are micronized with PSD D90 of equal to or less than 20 um,

dry blending, wet granulating, or roller compacting the resulting mixture, and

filling into capsules the dry blended, wet granulated, or roller compacted mixture, or compressing into tablets the dry blended, wet granulated, or roller compacted mixture.

[032] In some embodiments of the method of preparing a tablet or capsules, the Compound A, pharmaceutically acceptable salts thereof, and Forms I and II of Formula A are micronized with PSD D90 value ranging from 1.0-20.0 μm, or ranging from 2.0-12.0 μm. In some embodiments of the method of preparing a tablet or capsules, the Compound A, pharmaceutically acceptable salts thereof, and Forms I and II of Formula A are micronized with PSD D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments of the method of preparing a tablet or capsules, the Compound A, pharmaceutically acceptable salts thereof, and Forms I and II of Formula A are micronized with PSD D90 value ranging from 2.0 to 5.0 μm, for example, with a D90 value as 3.0, 3.5, or 4.0 μm. In some embodiments of the method of preparing a tablet or capsules, the Compound A, pharmaceutically acceptable salts thereof, and Forms I and II of Compound A are micronized with PSD D90

value ranging from 9.0 to 12.0 μm, for example, with a D90 value as 9.5 or 10.0 μm.

BRIEF DESCRIPTION OF THE DRAWINGS

[033] FIG. 1 shows anti-tumor effects of Compound A in NCI-H716 tumor model.

[034] FIG. 2 shows PK profiles of Compound A in dogs of Group 1 after a single PO dosing of Capsule A in Period 1.

[035] FIG. 3 shows PK profiles of Compound A in dogs of Group 1 after a single PO dosing of Capsule B in Period 2.

[036] FIG. 4 shows PK profiles of Compound A in dogs of Group 2 after a single PO dosing of Capsule B in Period 1.

[037] FIG. 5 shows PK profiles of Compound A in dogs of Group 2 after a single PO dosing of Capsule A in Period 2.

[038] FIG. 6 shows Mean concentration-time profiles of Compound A in dog plasma after single PO dosing of Compound A capsules comprising different formulations (n=6, only the animals without emesis).

[039] The following abbreviations and terms have the indicated meanings throughout:

[040] Unless clearly indicated otherwise, use of the terms "a", "an" and the like refers to one or more.

[041] The term “D90 value” refers to 90% (by numbers or volume) of the particles have a size that is less than or equal to the value. For example, D90 value of 20.0 μm means 90% (by numbers or volume) of the particles is less than

or equal to 20.0 μm in size; D90 value of 10.0 μm means 90% (by numbers or volume) of the particles is less than or equal to 10.0 μm in size.

[042] "Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, such as hydrochlorate, hydrobromate, phosphate, diphosphate,, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, maleate, mandelate, fumarate, tartrate, succinate, citrate, aspartate, glutamate, atrolactate, gluconate, propionate, lactate, camphorsulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, hydroxybutyrate, benzoate, salicylate, stearate, and alkanoate such as acetate, HOOC-(CH_2)n-COOH where n is 0-4, and like salts. Similarly, pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium.

[043] In addition, if a compound described herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used within the realm of routine experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

[044] The term "effective amount" of the compound of Formula A, including the novel form, described herein means an amount effective, when administered to a subject in recognized need, such as a human or non-human patient, to

alleviate the symptoms or stop the progression of at least one disease responsive to FGFR1 inhibition, such as cancer, and/or at least one disease responsive to KDR inhibition, such as angiogenesis-related disorders.

[045] The term "substantially pure Form I" refers to Compound A wherein at least 75 % by weight of Compound A is Form I. For example, substantially pure Form I" refers to Compound A wherein at least 75 %, 80%, 85%, 90%, or 95% by weight of Compound A is Form I. The definition also correspondingly applies to the term "substantially pure Form II."

Pharmaceutical Composition and Methods of Treatment

[046] In some embodiments, at least one active pharmaceutical ingredient chosen from the compound of Formula A (Compound A) and/or pharmaceutically acceptable salts thereof, and Forms I and II of the compound of Formula A may be useful for the treatment of neuroendocrine tumors.

[047] In some embodiments, the method of treating a subject having neuroendocrine tumors and in recognized need of treatment therefor comprises administering to said subject an effective amount of at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof, and Forms I and II of the compound of Formula A to treat said neuroendocrine tumors.

[048] In some embodiments, the method of treating a subject having neuroendocrine tumors and in recognized need of treatment therefor comprises administering to said subject an effective amount of Form I *N*-(2-(dimethylamino)ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide, to treat said neuroendocrine tumors .

[049] In some embodiments, the method of treating a subject having neuroendocrine tumors and in recognized need of treatment therefor comprises administering to said subject an effective amount of Form II *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide, to treat said neuroendocrine tumors.

[050] In some embodiments, the method of treating a subject having neuroendocrine tumors and in recognized need of treatment therefor comprises administering to said subject in recognized need of treatment an effective amount of a pharmaceutical composition comprising: at least one pharmaceutically acceptable carrier and the compound of Formula A and/or pharmaceutically acceptable salts thereof, to provide said treatment.

[051] In some embodiments, the method of treating a subject having neuroendocrine tumors and in recognized need of treatment therefor comprises administering to said subject an effective amount of a pharmaceutical composition comprising: at least one pharmaceutically acceptable carrier and Form I *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl), to provide said treatment.

[052] In some embodiments, the method of treating a subject having neuroendocrine tumors and in recognized need of treatment therefor comprises administering to said subject an effective amount of a pharmaceutical composition comprising: at least one pharmaceutically acceptable carrier and Form II *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methane- sulfonamide, to provide said treatment.

[053] In all embodiments disclosed herein above and hereinafter, Compound A, at least one pharmaceutically acceptable salt thereof, Form I, and Form II *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide, and substantially pure Form I and Form II *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide can be micronized, for example, with a D90 value of less than or equal to 20.0 μm, such as ranging from 1.0- 20.0 μm, or ranging from 2.0-12.0 μm, further such as from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm. In some embodiments, the D90 value ranges from 2.0 to 5.0 μm, for example, the D90 value is 3.0, 3.5, or 4.0 μm. In some embodiments, the D90 value ranges from 9.0 to 12.0 μm, for example, the D90 value is 9.5 or 10.0 μm.

[054] The amount of the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A effective for achieving the desired biological effect may depend on a number of factors, for example, the intended use, the mode of administration, and the clinical condition of the patient. The daily dose may, for example, range from 0.1 mg to 3 g/day (such as from 0.5 mg to 2 g /day, further such as from 50 mg to 1g /day). Single-dose formulations which can be administered orally include, for example, tablets or capsules. Further for example, the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable

salts thereof and Forms I and II of the compound of Formula A can be present in an amount of 1, 5, 10, 15, 20, 25, 50, 75, 80, 85, 90, 95, 100, 125, 150, 200, 250, 300, 400 and 500 mg in a capsule or tablet.

[055] For the therapy of the above-mentioned conditions, the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A may be used as the compound itself, but typically each of them would be used in the form of a pharmaceutical composition with one or more acceptable carriers/excipients. Representative carriers/excipients should be compatible with the other ingredients of the composition and not harmful for the patient's health. The carrier/excipient may be a solid or a liquid or both and may be formulated with the compound of Formula A, such as Form I and/or Form II described herein, as a single dose, for example as a tablet, which may be prepared from 0.05% to 95% by weight of the compound of Formula A described herein. The pharmaceutical compositions described herein can be produced by known pharmaceutical methods, such as those involving mixing the ingredients with pharmacologically acceptable carriers and/or excipients and/or diluents.

[056] In some embodiments, representative carriers/excipients would include but are not limited to: fillers (such as cellulose, starch, lactose, mannitol, dextrin, sorbitol, etc.), surfactants (such as sodium lauryl sulfate, poloxamer, etc.), solubilizers (such as polyvinylpyrrolidone, polyethylene glycol, etc.) , disintegrants (such as sodium starch glycolate, PVPP, Croscarmellose, etc.) and glidant and lubricant (such as SiO_2, magnesium stearate, etc.). Further exemplary carriers/excipients include microcrystalline cellulose, sodium citrate,

calcium carbonate, dicalcium phosphate, glycine, disintegrants such as starch, sodium cross-linked carboxymethyl cellulose, composite silicates, and polyethylene glycol with high moleculr weight, granulation binders (such as polyvinylpyrrolidone, sucrose, gelatin, and Gum Arabic), and lubricants (such as stearic acid, sodium stearyl fumarate and talc).

[057] In some embodiments, the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A may be combined with at least one component, such as carrier and/or excipient and/or diluent, chosen from sweeteners, delicate flavor agents, coloring matters, dyes, and emulsifiers.

[058] In some embodiments, the Form I or Form II described herein may not be converted upon formulation with the one or more pharmaceutically acceptable diluents. In other embodiments, the Form I or Form II described herein may be converted, in whole or in part, to one or more other forms, including a non-solid form, upon formulation with the one or more pharmaceutically acceptable carriers/diluents/excipients. Exemplary carriers/diluents/excipients would include but are not limited to, water, ethanol, propylene glycol, glycerine, and mixtures thereof. In some embodiments, the Form I or Form II described herein can be dissolved when formulated into a pharmaceutical composition. Accordingly, in such “dissolved” cases, the Form I or Form II no longer exists in their respective crystalline forms in the pharmaceutical composition.

[059] In some embodiments, the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically

acceptable salts thereof and Forms I and II of the compound of Formula A may be formulated to a suitable form.

[060] Pharmaceutical compositions described herein can be those suitable for oral and peroral (for example sublingual) administration, although the suitable mode of administration may depend in each individual case on the nature and severity of the condition to be treated and on the nature of the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A used in each case to prepare the pharmaceutical composition. Coated formulations and coated slow-release formulations also are provided. Acid- and gastric juice-resistant formulations are possible. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, anionic polymers of methacrylic acid, and methyl methacrylate.

[061] Suitable pharmaceutical compositions for oral administration prepared from the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A may be in the form of separate units such as, for example, capsules, cachets, and tablets, including suckable tablets, each of which may be prepared with a defined amount of the at least one active pharmaceutical ingredient described herein; as well as in the forms chosen from powders, granules, solutions, suspensions in an aqueous or nonaqueous liquid, and oil-in-water and water-in-oil emulsions. Those compositions may, as already mentioned, be prepared by any suitable pharmaceutical formulation

method, such as those including a step wherein the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A and a carrier (which may consist of one or more additional ingredients, including diluents and excipients) are brought into contact. The compositions can generally be produced by uniform and homogeneous mixing of the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A with a liquid and/or finely divided solid carrier, after which the product can be shaped. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A in powder form and then moistening with an inert liquid diluent, in a suitable machine. Compositions

can also be prepared by wet granulation. Thus, for example, a composition can be prepared by wet granulation by mixing the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A with one or more optional additional ingredients, a suitable solvent, and a binder to prepare a wet granulate, drying the wet granulate, and milling the dried granulate. The method may further comprise adding at least one lubricant to the dried milled granulate and compressing the dried milled granulate to form tablets. The optional additional ingredients may include, for example, at least one diluent and/or at least one disintegration agent. The suitable solvent can be water. In some embodiments, the diluent is chosen from calcium carbonate, calcium phosphate (dibasic and/or tribasic), calcium sulfate, powdered cellulose, dextrates, dextrin, fructose, kaolin, lactitol, anhydrous lactose, lactose monohydrate, maltose, mannitol, microcrystalline cellulose, sorbitol, sucrose, and starch. In some embodiments, the diluent can be present in an amount from about 35% to about 90% by weight of the tablet. In some embodiments, the binder can be chosen from acacia, alginic acid, carbomer, sodium carboxymethylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydroxypropyl cellulose, maltose, methylcellulose, polyethylene oxide, and povidone. In some exemplary embodiments, the binder is present in an amount of about 0.5% to about 5% by weight of the tablet. In other exemplary embodiments, the above-mentioned preparations contain about 0.05-5 g of the at least one active pharmaceutical ingredient chosen from the compound of

Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A per milliliter or per gram of the preparations.

[062] The compositions disclosed herein can be administered topically or systemically.

[063] Pharmaceutical compositions which are suitable for peroral (sublingual) administration can comprise suckable tablets which can be prepared from the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A ,with a flavoring agent, normally chosen from sucrose, gum arabic, tragacanth, and pastilles.

[064] Pharmaceutical compositions described herein can also be those suitable for parenterally administration, by inhalation spray, or via an implanted reservoir. Solid carriers, for example, starch, lactose, Microcrystalline Cellulose, aluminum silicate, liquid carriers, for example, injectable water, polyvinyl alcohol, non-ionized surfactant agents, and corn oil, and any ingredients suitable for intend use. Other excipients commonly used in pharmaceutical formulation include coloring agents, preservatives, taste correctives agents and antioxidants such as vitamin E, vitamin A, BHT and BHA.

[065] The compound of Formula A, such as the Form I or Form II described herein, can also be administrated intraperitoneally. And the solution and suspension of those compounds can be prepared by dissolving or suspended the compound in water containing suitable surfactants. Dispersed suspensions can be prepared by using glycerol, polyethylene glycol (PEG) or their mixture with

suitable oils. Preservatives agents can be added to those formulations to prevent growth of microorganisms during use.

[066] Injectable formulations include solution or suspension in sterilized water, and sterilized powder. In all cases, those formulations must be sterilized and easily removed from the syringe, and stable under the manufacture and storage conditions, and as free as possible from pollution and the effects of microorganisms. Carriers can be solvents or dispersing agents, and include water, alcohol, and some suitable oils.

[067] The at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A can also be administered in combination with one or more other active ingredients. When administered as a combination, the active ingredients can be formulated as separate compositions that are administered at the same time or sequentially at different times, or the active ingredients can be administered in a single dosage form, i.e., single composition, provided that the active ingredients are not, in that single dosage form, incompatible with other active ingredients or the formulation, or otherwise undesirably combined in a single composition.

[068] In some embodiments, the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A can be administered with one or more other agents known for the treatment of at least one disease responsive to FGFR1 inhibition, such as cancer, and/or at least one disease responsive to KDR inhibition, such as angiogenesis-related disorders.

[069] The phrase “co-therapy” (or “combination-therapy”) or “in combination with”, as used herein, defines the use of the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A as described herein and one or more other active ingredients, such as, for example, anti-neoplastic agents. As used herein, the term "anti-neoplastic agent" refers to any agent that is administered to a subject with cancer for purposes of treating the cancer. Non-limiting examples anti-neoplastic agents include: radiotherapy; immunotherapy; DNA damaging chemotherapeutic agents; and chemotherapeutic agents that disrupt cell replication.

[070] Non-limiting examples of DNA damaging chemotherapeutic agents include topoisomerase I inhibitors (e.g., irinotecan, topotecan, camptothecin and analogs or metabolites thereof, and doxorubicin); topoisomerase II inhibitors (e.g., etoposide, teniposide, and daunorubicin); alkylating agents (e.g., melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, methotrexate, mitomycin C, and cyclophosphamide); DNA intercalators (e.g., cisplatin, oxaliplatin, and carboplatin); DNA intercalators and free radical generators such as bleomycin; and nucleoside mimetics (e.g., 5-fluorouracil, capecitibine, gemcitabine, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and hydroxyurea).

[071] Chemotherapeutic agents that disrupt cell replication include: paclitaxel, docetaxel, and related analogs; vincristine, vinblastin, and related analogs; thalidomide and related analogs (e.g., CC-5013 and CC-4047); protein tyrosine kinase inhibitors (e.g., imatinib mesylate and gefitinib); proteasome inhibitors

(e.g., bortezomib); NF-kappa B inhibitors, including inhibitors of I kappa B kinase; antibodies which bind to proteins overexpressed in cancers and thereby downregulate cell replication (e.g., trastuzumab, rituximab, cetuximab, and bevacizumab); and other inhibitors of proteins or enzymes known to be upregulated, over-expressed, or activated in cancers, the inhibition of which downregulates cell replication.

[072] In co-therapy, administration of each active ingredient can occur in a sequential manner in a regimen to provide beneficial effects of the drug combination; and/or co-administration of the aforementioned components can occur in a substantially simultaneous manner (e.g., as in a single dosage form, such as a capsule, having a fixed ratio of the active ingredients or in multiple, separate capsules for each active ingredient, etc.).

[073] Thus, methods described herein are not limited in the sequence of administration; the at least one active pharmaceutical ingredient chosen from the compound of Formula A and/or pharmaceutically acceptable salts thereof and Forms I and II of the compound of Formula A described herein may be administered either prior to, at the same time with or after administration of the one or more other active ingredients.

[074] The following non-limiting examples are provided.

Example 1: Formulations

[075] Unless otherwise indicated, the micronized Compound A referred in the following formulation examples is substantially pure Form I.

[076] Formulation 1-Wet granulation

[077] The 200 mg capsule formulation was prepared from 500 gram of the micronized Compound A (PSD，D90= 9.6μm), 277.5 grams of mannitol, 150 grams of microcrystalline cellulose, 50 grams of sodium starch glycolate, 12.5 grams of polyvinylpyrrolidone (PVP) K30, and 10 grams of magnesium stearate. The micronized Compound A (500 g, D90=9.6 μm), mannitol (277.5 g), microcrystalline cellulose(150 g), and sodium starch glycolate (50 g) were mixed together. PVP-K30 (12.5 g) in a 5% (W/V) aqueous solution was prepared and added as binder to prepare granules by wet granulation process. Magnesium stearate (10 g) were added and blended for 3 minutes. 400 mg of the final blend was filled into a size#0 capsule to prepare Compound A 200 mg capsule products.

[078] Capsules of other dosages were prepared similarly. For example, 50 mg capsule of the micronized Compound A (D90=9.6μm) was prepared by filling 100 mg of a final blend prepared in a manner similar to the above into a size #3 capsule.

Table 1. The formulation examples by wet granulation process

	200mg capsule	50mg capsule
Compound A	200mg	50mg
Manitol	111mg	27.75mg
Microcrystalline Cellulous	60mg	15mg
Sodium Starch Glycolate	20mg	5mg
Povidone (PVP)	5mg	1.25mg
Magnesium stearate	4mg	1mg

[079] The 50 mg capsule formulation was prepared from 15 gram of the micronized Compound A (PSD，D90=3.8μm),19.9875 grams of mannitol, 6.75 grams of microcrystalline cellulose, 2.25 grams of sodium starch glycolate, 0.5625 grams of polyvinylpyrrolidone (PVP) K30, and 0.45 grams of magnesium

stearate. The micronized Compound A (Form I, 15 g, D90=3.8 μm), mannitol (19.9875 g), microcrystalline cellulose(6.75 g), and sodium starch glycolate (2.25 g) were mixed together. PVP-K30 (0.5625 g) in a 3% (W/V) aqueous solution was prepared and added as binder to prepare granules by wet granulation process. After the resulting wet granules were dried, magnesium stearate (0.45 g) was added to the dried granules and then blended for 3 minutes. 150 mg of the final blend was filled into a size#3 capsule to prepare Compound A 50 mg capsule products.

[080] The 50mg capsule formulation was prepared from 5 gram of the micronized Compound A (PSD，D90=3.8μm),15.37 grams of mannitol, 5.6 grams of microcrystalline cellulose, 1.4 grams of sodium starch glycolate, 0.35 grams of polyvinylpyrrolidone (PVP) K30, and 0.28 grams of magnesium stearate. The micronized Compound A (5 g, D90=3.8 μm), mannitol (15.37 g), microcrystalline cellulose(5.6 g), and sodium starch glycolate (1.4 g) were mixed together. PVP-K30 (0.35 g) in a 3% (W/V) aqueous solution was prepared and added as binder to prepare granules by wet granulation process. After the wet granules were dried, magnesium stearate (0.28g) was added to the dried granules and then blended for 3 minutes. 280 mg of the final blend was filled into a size#1 capsule to prepare Compound A 50 mg capsule products.

Table 2. The formulation examples by wet granulation process

	50mg capsule	50mg capsule
Compound A	50mg	50mg
Manitol	66.625mg	153.7mg
Microcrystalline Cellulous	22.5mg	56mg
Sodium Starch Glycolate	7.5mg	14mg
Povidone (PVP)	1.875mg	3.5mg
Magnesium stearate	1.5mg	2.8mg

[081] The capsules were analyzed for the release rate of active ingredient into 900 ml aqueous media (USP pH 4.5 acetate buffer) at 75 rpm rotation according to the first method (basket) described in the *China Pharmacopedia* (2010 Edition) or the method described in the *United State Pharmacopoeia* (USP) Dissolution Apparatus I. The accumulative release of Compound A from the capsules was above 70% at 0.5 hour.

[082] Formulation 2 - Direct mixing

A. 50 mg Capsule

[083] Micronized Compound A (150 g, D90=10.0μm) and microcrystalline cellulose (238.05 g) were sifted and mixed homogenously. Then magnesium stearate (1.95 g) was added and blended. 130 mg of the final blend was filled into a size #3 capsule to prepare 50 mg Compound A capsule products.

[084] Alternatively, micronized Compound A (25 g, D90=3.5 μm) and microcrystalline cellulose (39.675 g) were sifted and mixed homogenously. Then magnesium stearate (0.325 g) was added and blended. 130 mg of the final blend was filled into a size #3 capsule to prepare 50 mg Compound A capsule products.

[085] Further alternatively, micronized Compound A (25 g, D90=5.1 μm) and microcrystalline cellulose (39.675 g) were sifted and mixed homogenously. Then magnesium stearate (0.325 g) was added and blended. 130 mg of the final blend was filled into a size #3 capsule to prepare 50 mg Compound A capsule products.

B. 200 mg capsule

[086] Micronized Compound A (200 g, D90=10.0 μm), microcrystalline cellulose (178 g), sodium starch glycolate (9 g), and silicon dioxide (9 g) were sifted and mixed homogenously. Then magnesium stearate (4 g) was added and

blended for 3 minutes. 200 mg of the micronized Compound A capsules was obtained by filling 400 mg of the final blend into a size #0 capsule.

Table 3. The formulation examples by direct mixing and filling process

	200mg capsule	50mg capsule
Compound A, Form I	200mg	50mg
Microcrystalline Cellulous	178mg	79.35mg
Sodium Starch Glycolate	9mg	-
Silicon dioxide	9mg	-
Magnesium stearate	4mg	0.65mg

C. 25 mg capsule

[087] Micronized Compound A (27.8 g, D90=3.3 μm) and microcrystalline cellulose (205.1 g) were sifted and mixed homogenously. Then magnesium stearate (0.67 g) was added and blended for 5 minutes. 210 mg of the final blend was filled into a size #1 capsule to prepare 25 mg Compound A capsule products.

Table 4. The formulation example by direct filling process

	25mg capsule
Compound A, Form I	25mg
Microcrystalline Cellulous	184.4mg
Magnesium stearate	0.6mg

[088] The capsules were analyzed for the release rate of active ingredient into 900 ml aqueous media (USP pH4.5 acetate buffer) at 75 rpm rotation according to the first method (basket) described in the *China Pharmacopedia* (2010 Edition) or the method described in the *United State Pharmacopoeia* (USP) Dissolution Apparatus I. The cumulative release of Compound A from the capsules was above 70% at 0.5 hour.

Example 2: Anti-tumor effect of Compound A in H716 xenograft model

[089] Human colorectal adenocarcinoma cell line NCI-H716 cell line was reported to have the characteristic of endocrine cells, such as Dopa decarboxylase activity and cytoplasmic dense core granules. To confirm neuroendocrine characteristics of this cell line, subcutaneous tumors of NCI-H716 were established in nude mice, and pathological diagnosis with hematoxylin and eosin (HE) staining and immunohistochemistry (IHC) staining were performed on tumor tissue from subcutaneous xenograft model. NCI-H716 cells showed a diffuse growth pattern morphologically. The neoplastic cells were uniform and had large nuclei frequently with prominent nucleoli. IHC staining displayed that the tumor tissue was positive for CgA(chromogranin A), Syn(synaptophysin) and CD56(neural cell adhesion molecule 1), which was an important standard for neuroendocrine tumor diagnosis. Ki-67index was around 80%. Based on the morphologic and immunohistochemistry findings, NCI-H716 xenograft could be considered as a neuroendocrine carcinoma.

Materials and methods

[090] Human tumor cell line: NCI-H716 cell line was purchased from ATCC (CCL-251™) and incubated in the medium of RPMI1640 (Rosewell Park Memorial Institute 1640) plus 10% fetal bovine serum (FBS) at 37℃ in a 5% CO_2 incubator.

[091] Animals: BALB/c athymic male mice (6-8 weeks) were purchased from Shanghai SLAC Laboratory Animal Co. Ltd. The mice were housed under specific pathogen free conditions. They were maintained in a 12 hour light and dark cycle with the temperature at 20~25°C and humidity of 40%~70% and given

free access to Co^{60} radiated-sterile diet and autoclaved sterile water. There were four mice in each cage.

[092] Test article and formulation: Compound A was dissolved in 0.5% CMC-Na, vortexed for 1-3 min, sonicated for 15 min and stored at 4ºC. Compound A was formulated at 2.0, 4.0 and 8.0 mg/mL and prepared once a week.

[093] Tumor cells inoculation and anti-tumor efficacy study: When NCI-H716 cells reached about 80-90% in confluence, they were detached by Trypsin-EDTA and collected after centrifugation, then suspended in serum free-medium. Each mouse was injected subcutaneously in the right lateral flank with 0.2 mL of cells suspension containing 5×10^6 tumor cells with Martrigel (1:1).

[094] When the NCI-H716 tumors grew to around average 300 mm^3, the tumor bearing mice were randomized to vehicle and Compound A treated groups. Compound A in 0.5% CMC-Na as prepared above was orally administered to mice at 20, 40 and 80 mg/kg twice daily for three weeks, and the vehicle group received 0.5% CMC-Na orally twice daily. The dosing volume was 10 mL/kg body weight. Tumor volume (TV) was measured two times per week by caliper for length and width, and calculated using the formula: $TV = width^2 \times length/2$.

[095] At the end of the study, tumors were harvested and tumor growth inhibition (TGI) and tumor weight inhibition (IR_{TW}) were calculated by the following equations, where V_0 were the data at day 0 (D0) (starting day) and Vt were the data at measurement day t (Dt):

$$TGI = [1-(V_t-V_0)_{drug\ treated} / (V_t-V_0)_{vehicle}]\times 100\%$$

$$IR_{TW}(\%)= [(TW_{vehicle}-TW_{treatment}) / TW_{vehicle}] \times 100\%$$

[096] Statistical Analysis: Student's t-test was used for in comparison with vehicle control. Differences were considered statistically significant at P <0.05.

Results

[097] As FIG. 1 indicated, Compound A demonstrated dose dependent anti-tumor effect in NCI-H716 model. At the end of study, H716 tumor growth was repressed by 57.1%, 73.9% and 80.0% at Compound A 20, 40 and 80 mg/kg bid, respectively. And Compound A also decreased tumor weight by over 60% at middle and high doses. Statistical significance was seen when Compound A treated group was compared with vehicle treated group (Table 5). No clinical signs of toxicity were observed in Compound A treated mice.

Table 5. Anti-tumor efficacy summary of Compound A in NCI-H716 tumor model

Group	TGI (%)	IR_{TW} (%)
Compound A-20, bid	57.1*	49.9*
Compound A-40, bid	73.9**	62.6**
Compound A-80, bid	80.0**	69.8**

*, P<0.05; **, P<0.01 *vs* vehicle

[098] NCI-H716 xenograft could be considered as a neuroendocrine carcinoma. Compound A inhibited NCI-H716 growth in a dose dependent manner, indicating that Compound A would have therapeutic potential for the treatment of neuroendocrine carcinomas or neuroendocrine tumors in clinic.

Example 3: Cell viability assay on NCI-H716

Cell line

NCI-H716: human cecum colorectal adenocarcinoma cell line, purchased from ATCC (American Type Culture Collection).

Culture medium: RPMI 1640 containing 10% FBS.

Materials and solution

Compound: Compound A (lot#100223, purity, 96.7%) was synthesized in Hutchison Medipharma Limited;

CCK-8 kit (Cell Counting Kit-8): Brand: Dojindo, Catalog No.CK04-01;

Microplate reader: Model: Labsystems Multiskan K3, Brand: Thermo.

Cells treatment

[099] NCI-H716 cells were diluted with RPMI-1640 medium containing 10% FBS. 90 μL of the diluted cells were added into each well of a 96-well plate. Each well contained 1×10^4 cells. The cells were subsequently incubated at 37°C, 5% CO_2 overnight.

[0100] Test compound dissolved in DMSO was diluted to 30, 10, 3.33, 1.11, 0.37, 0.12, 0.04, 0.01μM with serum free RPMI-1640 medium containing 5% DMSO. Then 10 μL of the diluted compound was added into the above 90 μL cell cultures (final concentration of DMSO in the reaction mixture should be 0.5%), and incubated at 37°C, 5% CO_2 for 72 h.

CCK-8 assay

[0101] 10μL of CCK-8 solution was added into cells, and incubated at 37°C, 5% CO_2 for additional 1h. The optical density of each well was measured at 450 nm and 630 nm, respectively, by Labsystems Multiskan K3.

Data analysis

$$\text{Inhibition}(\%) = 100 - \frac{[\text{OD compound}]_{450\text{-}630} - [\text{OD background}]_{450\text{-}630}}{[\text{OD cell}]_{450\text{-}630} - [\text{OD background}]_{450\text{-}630}} \times 100$$

$[OD\ compound]_{450\text{-}630}$: the optical density of well containing cells with compound treatment;

$[OD\ cell]_{450\text{-}630}$: the optical density of wells containing cells without compound treatment;

$[OD\ background]_{450\text{-}630}$: the optical density of wells containing culture medium only.

[0102] IC_{50}: IC_{50} is calculated based on the inhibition curve fitted by XL-Fit 2.0 software.

[0103] Result: IC_{50} of Compound A on inhibition of NCI-H716 cells viability was determined as 0.159 μM.

Example 4: Pharmacokinetics of Compound A in Beagle Dogs Following a Single Oral Administration of Two Different Capsule Formulations Comprising Compound A

[0104] This dog PK study included two periods, with a crossover study design and a washout period of 1 week. Twelve beagle dogs were divided to two groups, 3 males and 3 females for each group. The dosage was 30 mg/kg, one capsule each dog. In period 1, Group 1 was administered Capsule A (micronized Compound A formulation), and Group 2 was administered Capsule B (non-micronized Compound A formulation). Both Capsule A and Capsule B was filled with 130 mg of a 26 g mixture comprising 10.0 g Compound A, 15.87g microcrystalline cellulose, and 0.13 g magnesium stearate. In other words, each

Capsule A and Capsule B contained 50 mg Compound A. The difference between Capsule A and Capsule B is that Compound A in Capsule A is micronized Form I of Compound A with D90=9.5 μm whereas Compound A in Capsule B is non-micronized Form I of Compound A with D90=39.2 μm.

[0105] After one week's washout, Group 1 was administered Capsule B and Group 2 was administered Capsule A. Blood samples were collected at different time points after dosing. The detailed information of grouping and time points for blood collection is shown in Table 6.

Table 6 Grouping and time points for collection of blood samples

Period	Dosing Date	Group No.	Test article			
				Sample	Day	Time points
1	24-July-2012	1	Capsule A	Plasma	1^{st}, 2^{nd}	0, 15, 30 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24h
		2	Capsule B	Plasma	1^{st}, 2^{nd}	
2	31-July-2012	1	Capsule B	Plasma	1^{st}, 2^{nd}	
		2	Capsule A	Plasma	1^{st}, 2^{nd}	

[0106] The method of protein precipitation with acetonitrile containing phenacetin (internal standard, IS) was used for the dog plasma pretreatment. Compound A concentrations in plasma were determined by a liquid chromatography-tandem mass spectrometry (LC-MS/MS) under a gradient elution condition with Mobile Phase A (deionized water containing 0.1% formic acid) and Mobile Phase B (acetonitrile containing 0.1% formic acid).

Sample Analysis

[0107] Symmetry C18 column (2.1×50 mm, 3.5μm) was used for the sample analysis. Multiple reaction monitoring (MRM) and the positive mode with electrospray ionization (ESI) were applied, and the corresponding detection ions

(Q1/Q3) of Compound A were 481.2/329.3. PK parameters were calculated using the non-compartment analysis of Kinetica software. The bioequivalence for the two capsules was evaluated through the statistic tests on the exposure of Compound A in plasma with the confidence interval method and on the Tmax of Compound A in plasma with the Friedman rank sum test.

A. Preparation of stock solution and working solutions

[0108] Compound A powder (23.68 mg) was weighed and dissolved in 942 μL of DMSO. Vortex and ultrasonication were performed until the powder was dissolved completely. HMPL-012 primary stock solution was obtained at 25 mg/mL. Compound A stock solution (40 μL) was spiked into 960 μL acetonitrile. After vortex, Compound A secondary stock solution was obtained at 1.0 mg/mL.

B. Preparation of calibration curve and quality control samples

[0109] Calibration standard (C) or quality control (QC) working solution (10 μL) was spiked into 190 μL of plasma from naive dogs. After vortex for 1 min, the spiked plasma (50 μL) was transferred into a blank 1.5 mL tube. 150 μL of acetonitrile containing 500 ng/mL phenacetin (internal standard, IS) was added for protein precipitation. The tube was vortexed for 2 min, and then centrifuged in 14000 rpm at 4°C for 10 min. The supernatant (150 μL) was transferred into a 1.5 mL blank tube, and then 150 μL of deionized water was added. After vortex for 1 min, one aliquot of the final solution (10 μL) was used for analysis.

[0110] Blank sample was the same as the calibration curve samples except for acetonitrile instead of compound working solutions.

[0111] Double blank sample was the same as blank sample, except that the added acetonitrile solution did not contain phenacetin.

C. Preparation of plasma samples

[0112] Plasma sample (50 μL each) obtained from the animal experiment was transferred into a 1.5 mL blank tube, and 150 μL of acetonitrile containing 500 ng/mL phenacetin was added for protein precipitation. After vortex for 2 min, the mixture was centrifuged (14000 rpm at 4 oC for 10 min). The supernatant (150 μL) was transferred into a 1.5 mL blank tube, and then 150 μL of deionized water was added. After vortex for 1 min, one aliquot of the final solution (10 μL) was injected to LC-MS/MS system for analysis.

Data Analysis

[0113] The peak areas of Compound A and IS were integrated by software Analyst 1.4.1. Standard curves were obtained from standard samples by plotting the peak area ratios of Compound A to IS against the theoretical concentrations of HMPL-012. The regression curve of Compound A was linear with weighting coefficient of 1/x2. The theoretical concentrations of Compound A in calibration standards were 2.50, 5.0, 10, 20, 50, 200, 500 and 1000 ng/mL, respectively. The concentrations of Compound A in dog plasma samples were determined using the standard curves. Pharmacokinetic parameters were calculated based on the plasma concentration-time data, using Thermo Kinetica® software (Version 4.4.1, Thermo Electron Corporation). Non-compartment analysis was performed. The bioequivalence of the two capsules was evaluated through the statistic tests on the exposure of Compound A in dog plasma with confidence interval method and on the Tmax of Compound A in dog plasma with Friedman rank sum test.

Results

[0114] The PK profile of Compound A in each dog is shown in FIG. 2-FIG. 5. The average plasma concentrations of Compound A plotted against the time points are shown in FIG. 6.

[0115] The actual dosages for dogs 3#, 4#, 6#, 7#, 8# and 10# would be lower than designed according to the occurrence time of vomiting and the appearance of vomitus, so the PK results of these dogs were not used for the mean value calculation. The mean values of main Compound A PK parameters in dogs are showed in Table 7.

Table 7 Major PK parameters mean values of Compound A in dogs (n=6)

Parameter	Unit	Capsule A		Capsule B	
		Mean	SD	Mean	SD
Dosage	mg/kg	30	-	30	-
$T_{1/2}$	h	5.65	1.37	5.54	1.20
MRT	h	11.1	1.46	10.6	1.61
AUC_{0-24}	h·ng/mL	6753	2901	4644	3619
$AUC_{0-\infty}$	h·ng/mL	7388	3249	4976	3802
C_{max}	ng/mL	623	254	425	367
T_{max}	h	6.00	1.10	4.50	2.88

Note: the PK parameters of dogs 3#, 4#, 6#, 7#, 8# and 10# were not used for mean calculation due to the emesis after dosing. Capsule A contained micronized Compound A formulation. Capsule B contained non-micronized Compound A formulation.

[0116] Based on the PK profiles of Compound A and the cage-side observations, Capsule A had smaller inter-subject variability and less emesis cases in dogs than Capsule B. Compared with Capsule B, Capsule A had higher average exposure to Compound A after a single oral administration in dogs. There was no significant statistic difference in Tmax mean value in beagle dogs for Capsule A and Capsule B.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition, comprising

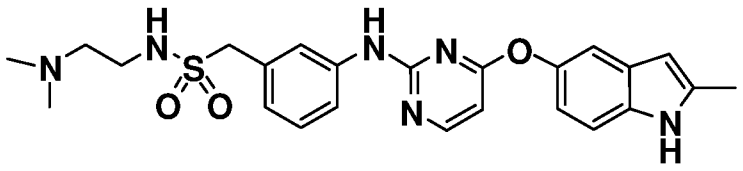
micronized Compound A , and/or

micronized at least one pharmaceutically acceptable salt thereof, and

at least one pharmaceutically acceptable carrier,

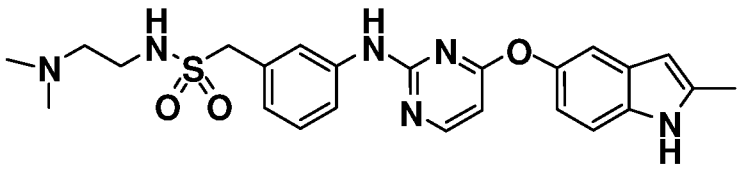
wherein the micronized Compound A and/or the micronized at least one pharmaceutically acceptable salt thereof has a particle size distribution (PSD) D90 value of less than or equal to 20 μm,

wherein Compound A is *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide having the structure:



2. A pharmaceutical composition, comprising at least one pharmaceutically acceptable carrier and micronized Compound A having a D90 value of less than or equal to 20 μm,

wherein Compound A is *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide having the following structure:



3. The pharmaceutical composition of claim 2, wherein the micronized Compound A is Form I *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide.

4. The pharmaceutical composition of claim 3, wherein the micronized Compound A is substantially pure Form I *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide.

5. The pharmaceutical composition of any of claims 2-4, wherein the micronized Compound A has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm.

6. The pharmaceutical composition of any one of claims 2-4, wherein the micronized Compound A has a D90 value ranging from 2.0 to 5.0 μm or ranging from 9.0 to 12 μm.

7. The pharmaceutical composition of claim 2, wherein the micronized Compound A is Form II *N*-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1*H*-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide.

8. The pharmaceutical composition of claim 7, wherein the micronized Compound A is substantially pure Form II N-(2-(dimethylamino) ethyl)-1-(3-((4-((2-methyl-1H-indol-5-yl)oxy)pyrimidin-2-yl)amino)phenyl)methanesulfonamide.

9. The pharmaceutical composition of claim 7 or 8, wherein the micronized Form II has a D90 value ranging from 1.0 to 2.0 μm, from greater than 2.0 to 3.0 μm, from greater than 3.0 to 4.0 μm, from greater than 4.0 to 6.0 μm, from greater than 6.0 to 8.0 μm, from greater than 8.0 to 10.0 μm, or from greater than 10.0 to 12.0 μm.

10. The pharmaceutical composition of claim 7 or 8, wherein the micronized Compound A has a D90 value ranging from 2.0 to 5.0 or ranging from 9.0 to 12 μm.

11. A method of treating a subject in recognized need of treatment for at least one disease responsive to FGFR1 inhibition, and/or at least one disease responsive to KDR inhibition, comprising administering to said subject in need thereof an effective amount of a pharmaceutical composition according to any one of claims 1-10.

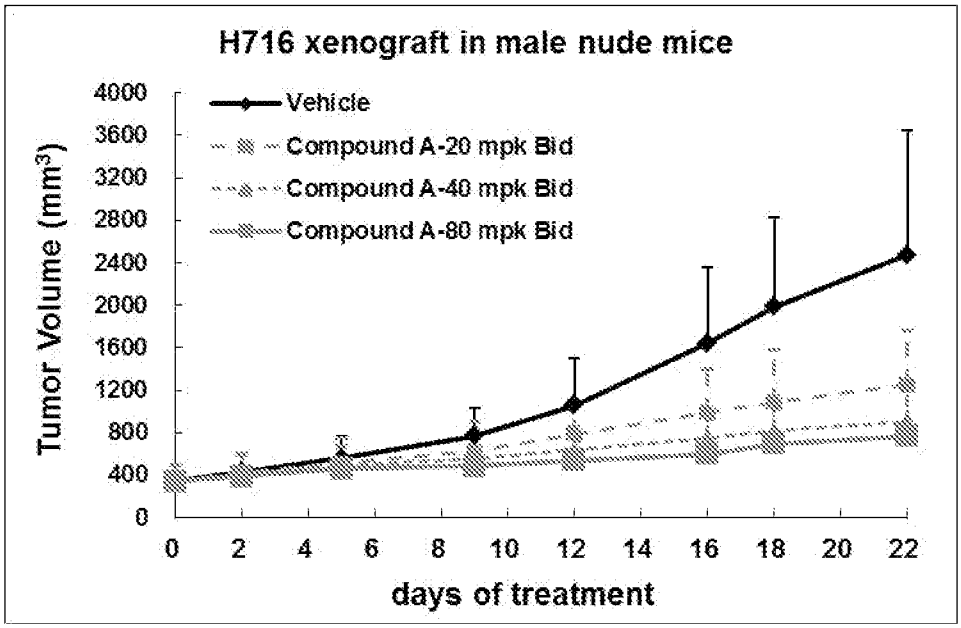


FIG.1. Anti-tumor effect of Compound A in NCI-H716 tumor model

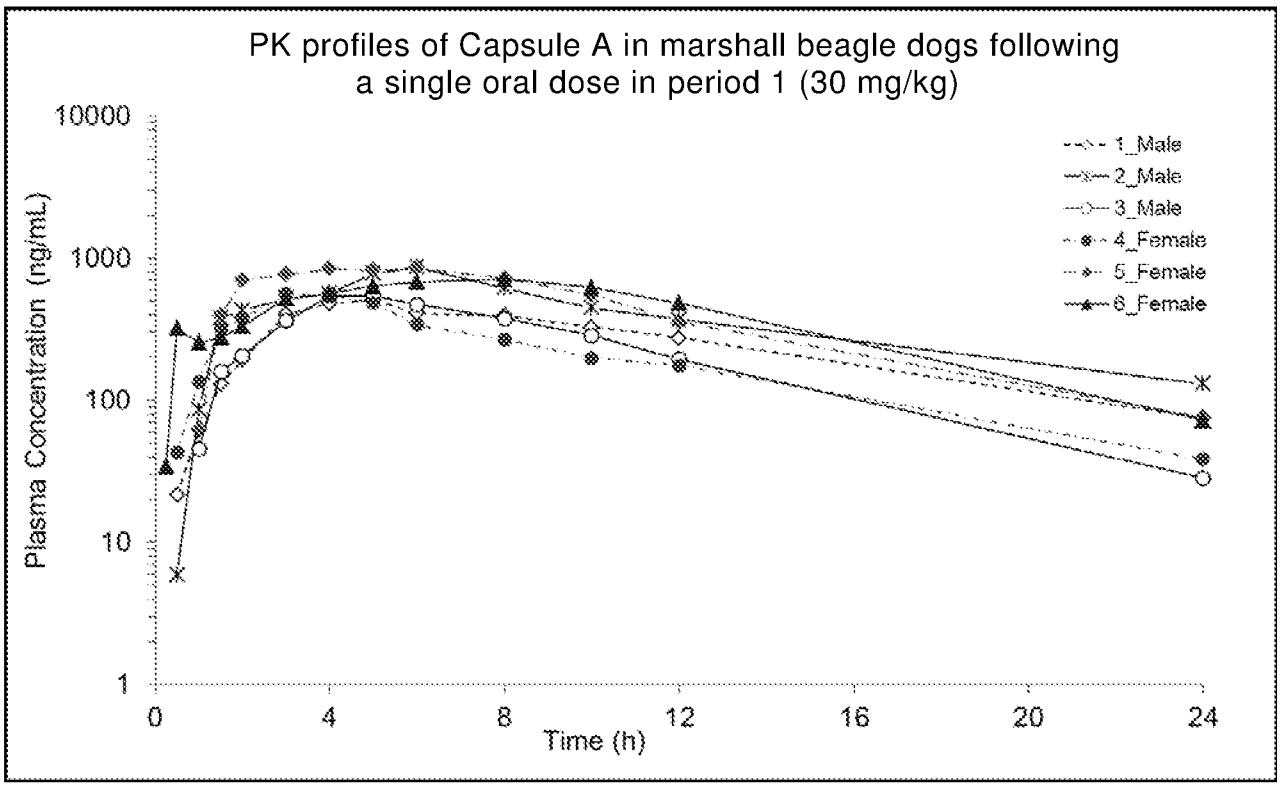


FIG.2. PK profiles of Compound A in dogs of Group 1 after a single PO dosing of Capsule A in Period 1.

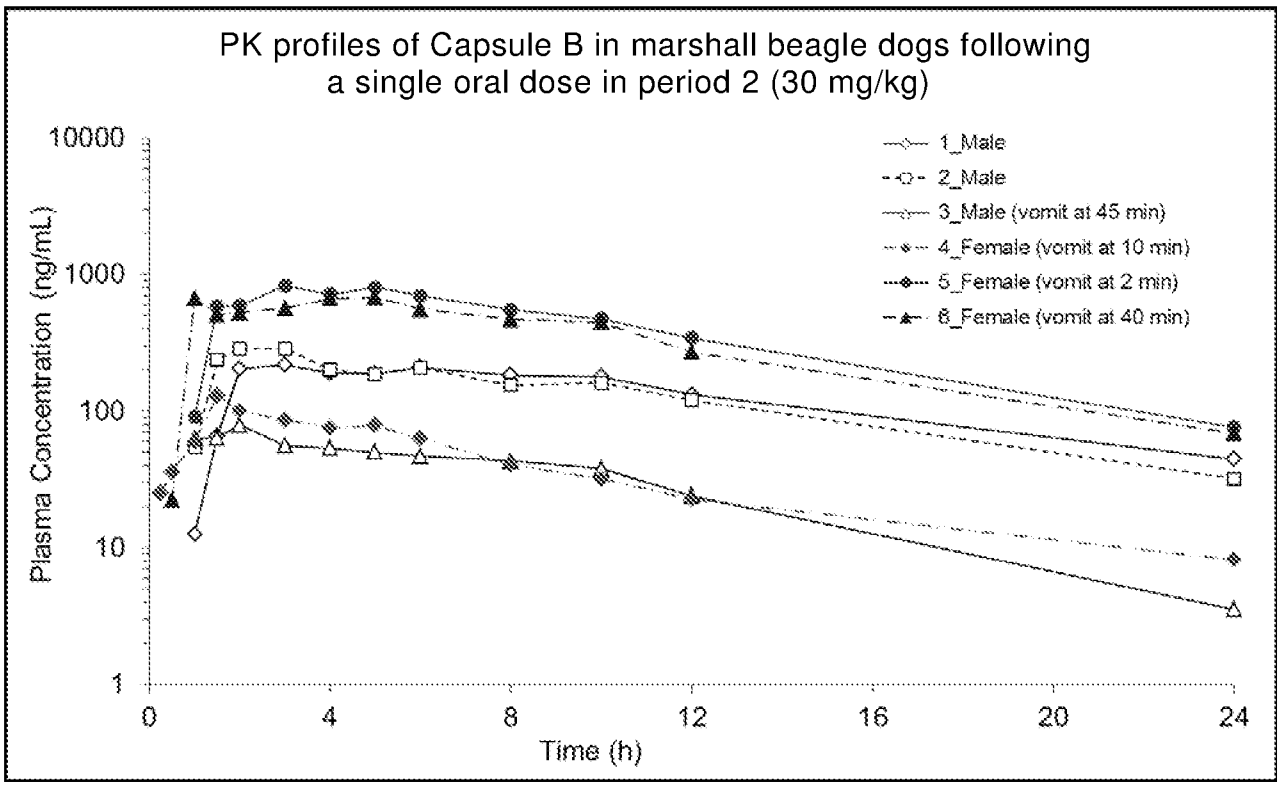


FIG.3. PK profiles of Compound A in dogs of Group 1 after a single PO dosing of Capsule B in Period 2.

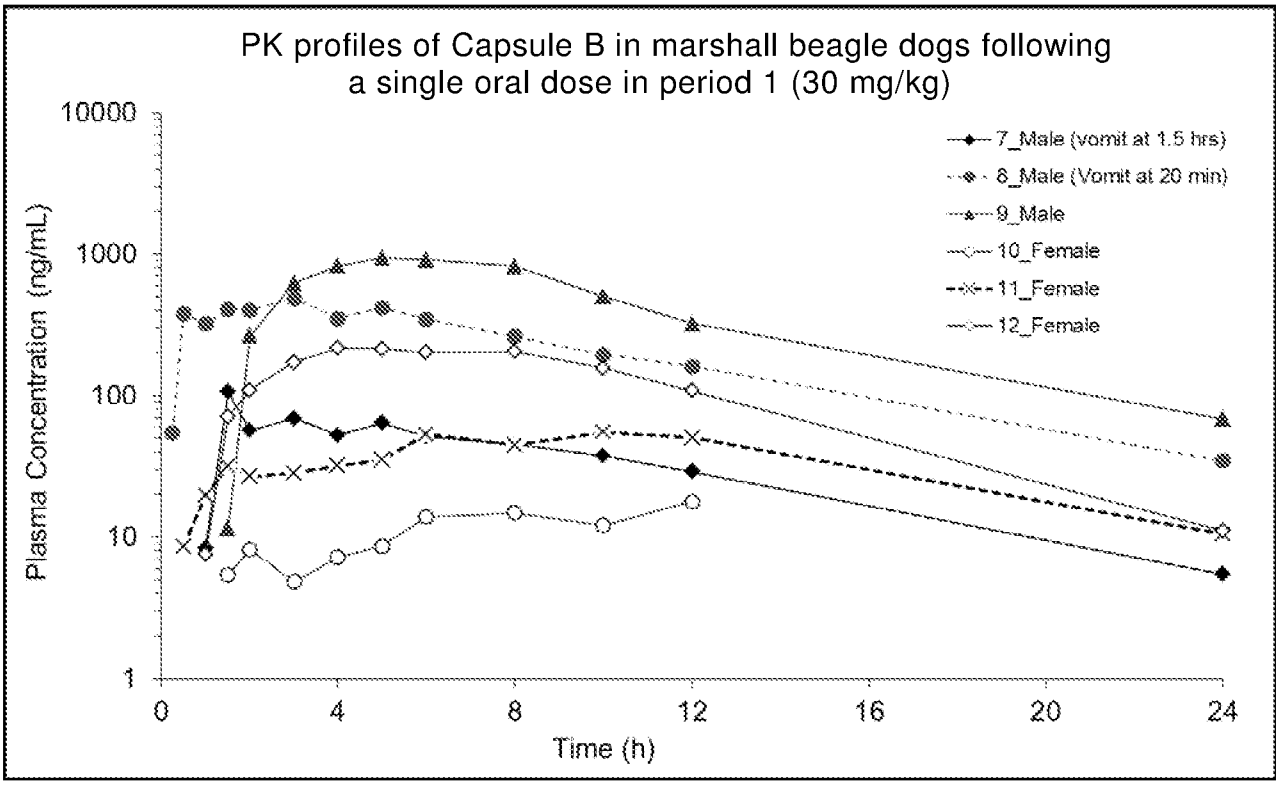


FIG.4. PK profiles of Compound A in dogs of Group 2 after a single PO dosing of Capsule B in Period 1.

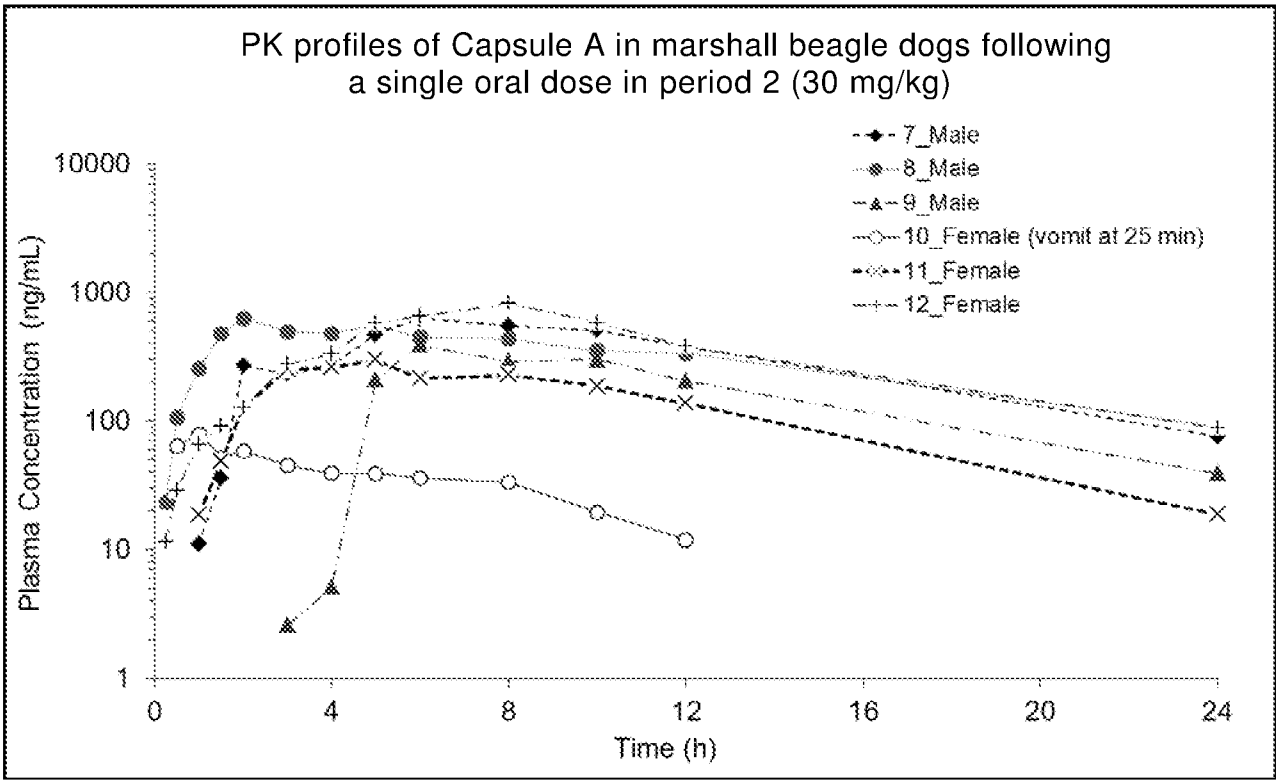


FIG. 5 shows PK profiles of Compound A in dogs of Group 2 after a single PO dosing of Capsule A in Period 2.

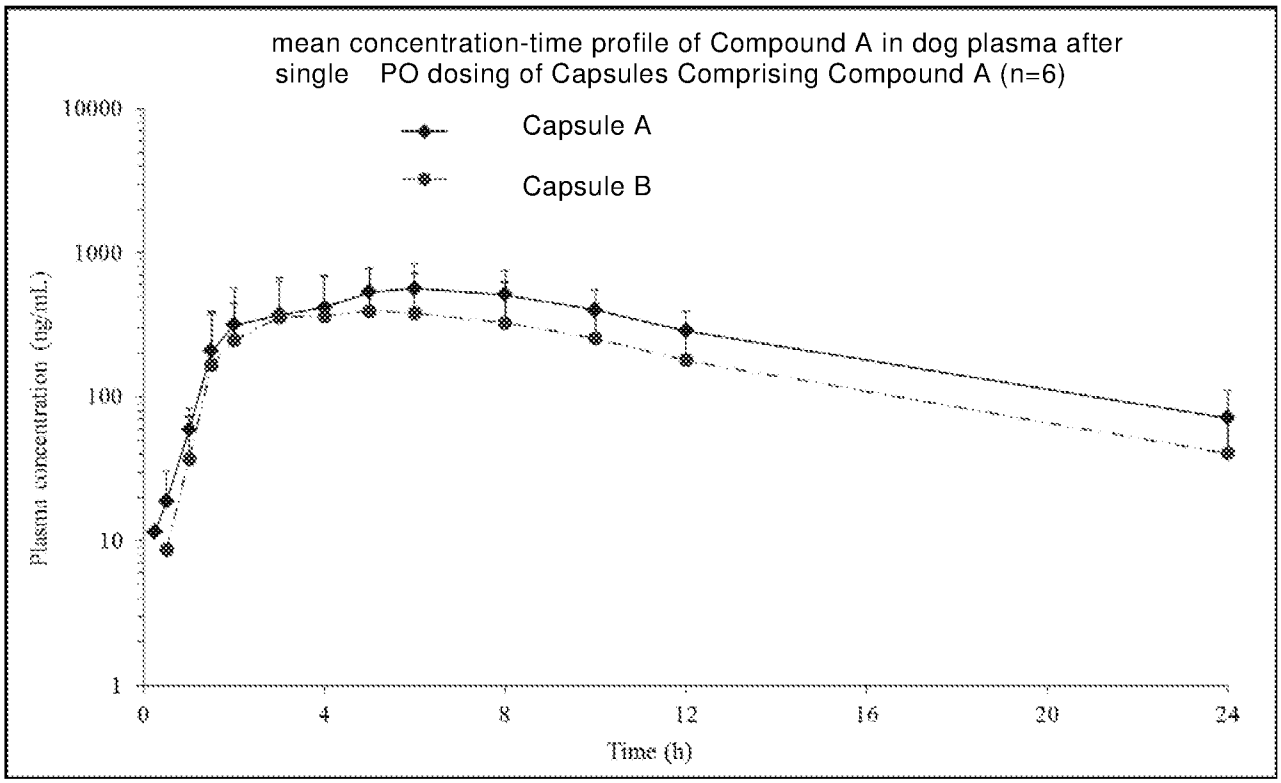


FIG.6. Mean concentration-time profiles of Compound A in dog plasma after single PO dosing of Compound A capsules comprising different formulations (n=6, only the animals without emesis)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/079650

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/513(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CNPAT(CN), CNKI(CN), Chinese Pharmaceutical Abstract (CN), CHEMICAL ABSTRACTS(US), EMBASE, STN: dimethylamino, pyrimidin, methanesulfonamide, particle, size, distribution, PSD, D90, fgfr1, kdr, inhibit+, cancer, structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 102070618 A (HUTCHISON MEDIPHARMA LTD) 25 May 2011 (2011-05-25) whole document	1-11

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2016	**01 March 2016**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/079650

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **11**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 11 relates to a method of treating one disease responsive to FGFR1 inhibition and/or at lease one disease responsive to KDR inhibition(PCT R39.1(iv)), but the search has been carried out and based on the reasonably anticipant subjects, i.e. the use of a pharmaceutical composition according to any one of claims 1-10 in manufacture of medicaments for treating one disease responsive to FGFR1 inhibition and/or at lease one disease responsive to KDR inhibition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/079650

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
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		CA 2781066 A1	26 May 2011
		AU 2010321366 A1	14 June 2012
		AU 2010321366 A8	05 July 2012
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		JP 2013511475 A	04 April 2013
		CN 102070618 B	21 August 2013
		SG 180938 A1	28 June 2012
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		US 8658658 B2	25 February 2014
		NZ 600266 A	27 June 2014
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		AU 2010321366 B2	24 July 2014
		CA 2781066 C	16 September 2014
		EP 2504331 B1	12 November 2014
		CN 102648194 B	29 October 2014
		US 8946249 B2	03 February 2015
		ES 2529105 T3	16 February 2015
		KR 101513784 B1	20 April 2015
		JP 5758399 B2	05 August 2015
		INDELNP 201204868 E	25 September 2015