Claims

[Claim 1] A pharmaceutical formulation comprising a plurality of centanafadine (CTN) beads, the plurality of CTN beads each comprising a core particle comprising CTN or a pharmaceutically acceptable salt thereof and an excipient.

[Claim 2] The pharmaceutical formulation of claim 1, wherein at least a portion of the core particles comprise CTN or a pharmaceutically acceptable salt thereof in an amount in a range of about 70 wt.% to about 90 wt.%.

[Claim 3] The pharmaceutical formulation of claim 1, wherein at least a portion of the plurality of beads comprise a coating which is one or more coatings selected from a delayed release coating, a sustained release coating, and a delayed-sustained release coating.

[Claim 4] The pharmaceutical formulation of claim 3, wherein the coating comprises a delayed release coating comprising one or more materials selected from amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/methyl methacrylate, co-polymerized methylacrylate/methyl methacrylate/methacrylic acid, hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, styrene maleic acid copolymer, and styrene vinylpyridine copolymer.

[Claim 5] The pharmaceutical formulation of claim 3, wherein the coating comprises a sustained release coating comprising one or more materials selected from an alkylcellulose, acrylic acid polymer, a methacrylic acid polymer, an acrylic acid copolymer, a methacrylic acid copolymer, and a cellulose ether.

[Claim 6] The pharmaceutical formulation of claim 3, wherein the coating further comprises a pore former.

[Claim 7] The pharmaceutical formulation of claim 6, wherein the pore former comprises one or more materials selected from hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol, poloxamer 188, polyvinylpyrrolidone, d-mannitol, methyl cellulose, polyvinyl alcohol-polyethylene glycol graft copolymer, and saccharide.

[Claim 8] The pharmaceutical formulation of claim 1, wherein the core particles are characterized by having a distribution of particles sizes, and at least a portion of the core particles of the plurality of beads have a core

particle size (maximum diameter) of about 0.2 mm to about 2 mm.

[Claim 9] The pharmaceutical formulation of claim 8, wherein the distribution of particles sizes of the core particles is characterized by at least 60% by weight of the core particles having a particle size (maximum diameter) in a range of about 0.4 mm to about 1.5 mm.

[Claim 10] The pharmaceutical dosage form of claim 1, wherein the plurality of CTN beads have a median particle size (diameter) in a range of about 0.2 mm to about 2.8 mm.

[Claim 11] The pharmaceutical formulation of claim 1, wherein the plurality of CTN beads comprises at least two types selected from an immediate release bead, a sustained release bead, a delayed release bead, and a delayed-sustained release bead.

[Claim 12] The pharmaceutical formulation of claim 11, wherein the plurality of beads comprises a mixture of one or more immediate release beads, one or more sustained release beads, and one or more delayed release beads.

[Claim 13] The pharmaceutical formulation of claim 12, wherein the ratio of CTN or pharmaceutically acceptable salt thereof is present in the one or more immediate release beads, one or more sustained release beads, and one or more delayed release beads at a ratio in a range of about 0.1-1 : 1-20 : 1-20 parts by weight based on the weight of the CTN or salt thereof.

[Claim 14] The pharmaceutical formulation of claim 12, wherein the immediate release beads are present in the formulation in an amount in a range of about 1% to about 75% based on the total weight of the plurality of CTN beads.

[Claim 15] The pharmaceutical formulation of claim 11 comprising sustained release beads, wherein the sustained release beads are present in the formulation in an amount in a range of about 5% to 80% based on the total weight of the plurality of CTN beads.

[Claim 16] The pharmaceutical formulation of claim 11 comprising delayed release beads, wherein the delayed release beads are present in the formulation in an amount in a range of about 5% to 80% based on the total weight of the plurality of CTN beads.

[Claim 17] The pharmaceutical formulation of claim 11 comprising a mixture of immediate release beads, sustained release beads, and delayed release beads, wherein at least 40% of the CTN or salt thereof is released from the mixture of beads at a time in a range of 3 hours to 5 hours, and at least 90% of the CTN or salt thereof is released from the mixture of

beads at a time in a range of 12 hours to 14 hours, according to USP <711> with Apparatus 1 (basket) at 37 °C +/- 0.5 °C at 100rpm, first in 1000ml of a 0.1N HCl solution for 2 hours, then 1000ml pH 7.4 buffered water at 37 °C +/- 0.5 °C at 100rpm for the remainder of the time.

[Claim 18] The pharmaceutical formulation of claim 11 comprising a mixture of immediate release beads, sustained release beads, and delayed release beads, wherein according to USP <711> using Apparatus I (basket) in 1000 mL 0.1N hydrochloric acid at 37 °C +/- 0.5 °C at 100rpm for 2 hours, followed by Apparatus I (basket) in 1000 mL pH 7.4 phosphate buffer solution at 37 °C +/- 0.5 °C) at 100rpm for 12 hours, the release profile is characterized by:
(a) release of about 24% to 48% CTN at the 3 hour mark.

[Claim 19] The pharmaceutical formulation of claim 11, wherein the formulation provides an adult subject with a centanafadine plasma concentration at 1 hour post-dose (C_{1hr}) of at least 150 ng/mL, or in a range of about 150 ng/mL to about 610 ng/mL.

[Claim 20] The pharmaceutical formulation of claim 11, wherein the formulation provides an adult subject with a concentration of centanafadine in the plasma at 12 hours after administration (C_{12h}) of at least 95 ng/mL or in a range of about 95 ng/mL to about 450 ng/mL.

[Claim 21] The pharmaceutical formulation of claim 11, wherein the formulation provides an adult subject with a concentration of centanafadine in the plasma at 16 hours after administration (C_{16h}) of less than 300 ng/mL or in a range of about 95 ng/mL to about 300 ng/mL.

[Claim 22] The pharmaceutical formulation of claim 11, wherein the formulation provides an adult subject with a centanafadine plasma concentration post-dose which remains at least 75 ng/mL, or in a range of about 75 ng/mL to about 1500 ng/mL over the time period 2 to 8 hours post-dose.

[Claim 23] The pharmaceutical formulation of claim 11, wherein the administration provides an adult subject with a cumulative centanafadine plasma exposure in the 24-hour period after administration (AUC_{0-24h}) of at least 2400 ng h/mL, or in a range of 2400 ng h/mL to 12500 ng h/mL.

[Claim 24] The pharmaceutical formulation of claim 11, wherein herein the formulation provides an adult subject with a cumulative centanafadine plasma exposure after administration (AUC_{0-inf}) of at least 2400 ng h/

mL or in a range of 2400 ng h/mL to 12500 ng h/mL.

[Claim 25] The pharmaceutical formulation of claim 17, wherein the formulation comprises centanafadine hydrochloride and provides an adult subject with a centanafadine plasma concentration at 1 hour post-dose (C_{1hr}) of at least 150 ng/mL, a centanafadine plasma concentration post-dose which remains at least 250 ng/mL over the time period 2 to 8 hours post-dose, and a concentration of centanafadine in the plasma at 16 hours after administration (C_{16h}) of less than 300 ng/mL.

[Claim 26] The pharmaceutical formulation of claim 1, wherein the CTN is present as a pharmaceutically acceptable salt or is present as a hydrochloride salt.

[Claim 27] The pharmaceutical formulation of claim 1, wherein the excipient comprises one or more materials selected from a filler and a binder, a glidant, a surfactant, a polymer coating, and a plasticizer.

[Claim 28] The pharmaceutical formulation of claim 1, wherein the excipient comprises one or more materials selected from lactose, mannitol, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, hypromellose, polyvinyl pyrrolidone, talc, polysorbate 80, glycerol monostearate, triethyl citrate, polyvinyl alcohol-polyethylene glycol graft copolymer, and silica.

[Claim 29] A method of treatment using a formulation according to claim 1, comprising administering a formulation according to claim 1 to an animal subject in need thereof.

[Claim 30] A method of making a pharmaceutical formulation comprising centanafadine (CTN) or a pharmaceutically acceptable salt thereof, the method comprising compounding the CTN or pharmaceutically acceptable salt thereof with a binder to make particles comprising CTN or pharmaceutically acceptable salt thereof having a defined particle size range, and disposing a coating over at least a portion of the particles.

CLAIMS

1. A pharmaceutical dosage form comprising a plurality of centanafadine regions,

wherein the plurality of centanafadine regions comprise centanafadine or a pharmaceutically acceptable salt thereof and an excipient;

wherein the plurality of centanafadine regions comprises a mixture of a collection of one or more immediate release regions and a collection of one or more sustained release regions;

wherein the centanafadine or a pharmaceutically acceptable salt thereof is present in a greater amount, by weight of the centanafadine or pharmaceutically acceptable salt thereof, in the collection of one or more sustained release regions than in the collection of one or more immediate release regions, and up to a ratio of 1:100 parts by weight of centanafadine or salt thereof, in the collection of one or more immediate release regions to the collection of one or more sustained release regions.

2. The pharmaceutical dosage form according to claim 1, wherein the centanafadine or a pharmaceutically acceptable salt thereof is present up to a ratio of about 1:50 parts by weight of centanafadine or salt thereof, in the collection of one or more immediate release regions to the collection of one or more sustained release regions.

3. The pharmaceutical dosage form according to claim 1, wherein the centanafadine or a pharmaceutically acceptable salt thereof is present up to a ratio of about 1:20 parts by weight of centanafadine or salt thereof, in the collection of one or more immediate release regions to the collection of one or more sustained release regions.

4. The pharmaceutical dosage form of claim 1, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

5. The pharmaceutical dosage form of claim 1, wherein the one or more sustained release regions comprise a sustained release coating comprising one or more materials

selected from an alkylcellulose, acrylic acid polymer, a methacrylic acid polymer, an acrylic acid copolymer, a methacrylic acid copolymer, and a cellulose ether.

6. The pharmaceutical dosage form of claim 5, wherein the sustained release coating comprises an ethyl acrylate and methyl methacrylate copolymer.

7. The pharmaceutical dosage form of claim 5, wherein the sustained release coating comprises an ethyl acrylate, a methyl methacrylate copolymer and a cellulose ether.

8. The pharmaceutical dosage form of claim 5, wherein the sustained release coating further comprises a pore former.

9. The pharmaceutical dosage form of claim 8, wherein the pore former of the sustained release coating comprises one or more materials selected from hydroxypropylcellulose, hydroxypropyl methylcellulose, polyethylene glycol, poloxamer 188, polyvinylpyrrolidone, d-mannitol, methyl cellulose, polyvinyl alcohol-polyethylene glycol graft copolymer, and saccharide.

10. The pharmaceutical dosage form of claim 1, wherein the excipient comprises one or more materials selected from a filler, a binder, a glidant, a surfactant, a polymer coating, a lubricant, a disintegrant, and a plasticizer.

11. The pharmaceutical dosage form of claim 1, wherein the plurality of centanafadine regions further comprises one or more delayed release centanafadine regions.

12. The pharmaceutical dosage form of claim 1, wherein the plurality of centanafadine regions comprise a plurality of beads each comprising a core particle comprising centanafadine or a pharmaceutically acceptable salt thereof and an excipient.

13. A pharmaceutical dosage form comprising a plurality of centanafadine regions, wherein the plurality of centanafadine regions comprises centanafadine or a

pharmaceutically acceptable salt thereof and an excipient;

wherein the plurality of centanafadine regions comprises a mixture of a collection of one or more immediate release regions and a collection of one or more delayed release regions,

wherein the centanafadine or a pharmaceutically acceptable salt thereof is present in a greater amount, by weight of the centanafadine or pharmaceutically acceptable salt thereof, in the collection of one or more delayed release regions than in the collection of one or more immediate release regions, and up to a ratio of about 1:100 parts by weight of centanafadine or salt thereof, in the collection of one or more immediate release regions to the collection of one or more delayed release regions.

14. The pharmaceutical dosage form according to claim 13, wherein the centanafadine or a pharmaceutically acceptable salt thereof is present up to a ratio of about 1:50 parts by weight of centanafadine or salt thereof in the collection of one or more immediate release regions to the collection of one or more delayed release regions.

15. The pharmaceutical dosage form according to claim 13, wherein the centanafadine or a pharmaceutically acceptable salt thereof is present up to a ratio of about 1:20 parts by weight of centanafadine or salt thereof in the collection of one or more immediate release regions to the collection of one or more delayed release regions.

16. The pharmaceutical dosage form of claim 13, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

17. The pharmaceutical dosage form of claim 13, wherein the one or more delayed release regions comprise a delayed release coating comprising one or more materials selected from amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate succinate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters, co-polymerized methacrylic acid/methyl methacrylate, co-polymerized methylacrylate/methyl methacrylate/methacrylic acid,

hydroxypropyl methylcellulose acetate succinate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, styrene maleic acid copolymer, emulsion of glyceryl monostearate, triethyl citrate, polysorbate 80, and styrene vinylpyridine copolymer.

18. The pharmaceutical dosage form of claim 17, wherein the delayed release coating comprises poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid).

19. The pharmaceutical dosage form of claim 17, wherein the delayed release coating comprises a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid in a molar ratio of about 7:3:1.

20. The pharmaceutical dosage form of claim 13, wherein the plurality of centanafadine regions further comprises one or more sustained release centanafadine regions.

21. The pharmaceutical dosage form of claim 13, wherein the plurality of centanafadine regions comprise a plurality of beads each comprising a core particle comprising centanafadine or a pharmaceutically acceptable salt thereof and an excipient.

22. The pharmaceutical dosage form of claim 1, wherein at least 40% of the centanafadine or salt thereof is released from dosage form at a time in a range of 3 hours to 5 hours, and at least 90% of the centanafadine or salt thereof is released from the dosage form at a time in a range of 12 hours to 14 hours, according to the United States Pharmacopeia <711> with Apparatus 1 (basket) at 37 ºC +/- 0.5 ºC at 100rpm, first in 1000ml of a 0.1N HCl solution for 2 hours, then 1000ml pH 7.4 buffered water at 37 ºC +/- 0.5 ºC at 100rpm for the remainder of the time.

23. The pharmaceutical dosage form of claim 1, wherein the dosage form comprises centanafadine hydrochloride and is to be administered to provide an adult subject with a centanafadine plasma concentration at 1 hour post-dose (C1hr) of at least 150 ng/mL, a centanafadine plasma concentration post-dose which remains at least 250 ng/mL over

the time period 2 to 8 hours post-dose, and a concentration of centanafadine in the plasma at 16 hours after administration (C16h) of less than 300 ng/mL.

24. The pharmaceutical dosage form of claim 1, wherein according to the United States Pharmacopeia <711> using Apparatus 1 (basket) in 1000 mL 0.1N hydrochloric acid at 37 ºC +/- 0.5 ºC at 100rpm for 2 hours, followed by Apparatus 1 (basket) in 1000 mL pH 7.4 phosphate buffer solution at 37 ºC +/- 0.5 ºC) at 100rpm for 12 hours, the release profile is characterized by a release of about 24% to about 48% centanafadine at the 3-hour mark.

25. The pharmaceutical dosage form of claim 1, wherein the dosage form is to be administered to provide an adult subject with a centanafadine plasma concentration at 1 hour post-dose (C1hr) of at least 150 ng/mL, or in a range of about 150 ng/mL to about 610 ng/mL.

26. The pharmaceutical dosage form of claim 1, wherein the dosage form is to be administered to provide an adult subject with a concentration of centanafadine in the plasma at 12 hours after administration (C12h) of at least 95 ng/mL or in a range of about 95 ng/mL to about 450 ng/mL.

27. The pharmaceutical dosage form of claim 1, wherein the dosage form is to be administered to provide an adult subject with a concentration of centanafadine in the plasma at 16 hours after administration (C16h) of less than 300 ng/mL or in a range of about 95 ng/mL to about 300 ng/mL.

28. The pharmaceutical dosage form of claim 1, wherein the dosage form is to be administered to provide an adult subject with a centanafadine plasma concentration post-dose which remains at least 75 ng/mL, or in a range of about 75 ng/mL to about 1500 ng/mL over the time period 2 to 8 hours post-dose.

29. The pharmaceutical dosage form of claim 1, wherein the dosage form is to be administered to provide an adult subject with a cumulative centanafadine plasma exposure in the 24-hour period after administration (AUC0-24h) of at least 2400 ng·h/mL, or in a range of 2400 ng·h/mL to 12500 ng·h/mL.

30. The pharmaceutical dosage form of claim 1, wherein the dosage form is to be administered to provide an adult subject with a centanafadine plasma concentration at 1 hour post-dose (C1hr) in a range of about 150 ng/mL to about 610 ng/mL; at 12 hours post-dose (C12h) in a range of about 95 ng/mL to about 450 ng/mL; at 16 hours post-dose (C16h) in a range of about 95 ng/mL to about 300 ng/mL; and wherein the ratio C16h/C12h is less than 1.