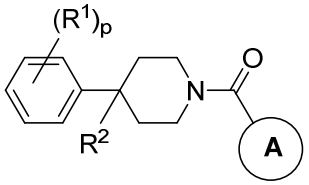
## CLAIMS

We Claim:

1. A pharmaceutical composition comprising a solid dispersion, wherein the solid dispersion comprises:

(i) a compound of Formula (I), a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:




Formula (I)

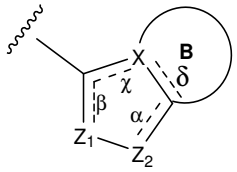
wherein:

each $R^1$ is independently halogen, haloalkyl, or alkyl;

$R^2$ is -H, -OH, or halogen;

p is 0, 1, 2, 3, 4, or 5;

**A** has the structure:




wherein:

α, β, χ, and δ are each independently absent or present, and when present each is a bond;

X is C;

$Z_1$ is S, O, or N;

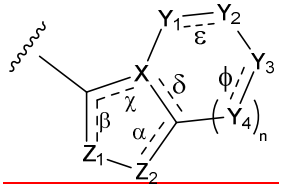
$Z_2$ is S, O, N, or $NR^3$;

$R^3$ is H, $C_1$-$C_4$ alkyl, or oxetane; and

B is a substituted or unsubstituted fused 5-, 6-, or 7- membered ring structure; and

(ii) a dispersion polymer.

~~2. The pharmaceutical composition of claim 1, wherein A has the structure~~



wherein:

n is 0, 1, or 2;

α, β, χ, δ, ε, and ϕ are each independently absent or present, and when present each is a bond;

$Z_1$ is S, O, or N;

$Z_2$ is S, O, N or $NR^3$;

wherein $R^3$ is H, $C_1$-$C_4$ alkyl, or oxetane;

X is C;

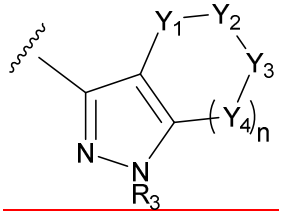
$Y_1$, $Y_2$, $Y_3$ and each occurrence of $Y_4$ are each independently $CR^4$, $C(R^5)_2$, $NR^6$, O, N, $SO_2$, or (C=O) , wherein:

$R^4$ is H, halogen, $C_1$-$C_{10}$ alkyl, $C_1$-$C_{10}$ cycloalkyl, $O(C_1$-$C_{10}$ alkyl), $C(O)OH$, $C(O)O(C_1$-$C_{10}$ alkyl), $C(O)NH_2$, $C(O)NH(C_1$-$C_4$ alkyl), $C(O)N(C_1$-$C_4$ alkyl)$_2$, $NHC(O)NH(C_1$-$C_{10}$ alkyl), $NHC(O)N(C_1$-$C_4$ alkyl)$_2$, $SO_2NH(C_1$-$C_{10}$ alkyl), $SO_2N(C_1$-$C_{10}$ alkyl)$_2$, CN, or $CF_3$;

$R^5$ is H or $C_1$-$C_{10}$ alkyl; and

$R^6$ is H, $C_1$-$C_{10}$ alkyl, $C_3$-$C_6$ cycloalkyl, $(C_1$-$C_{10}$ alkylene)$CF_3$, $(C_1$-$C_{10}$ alkylene)$OCH_3$, $(C_1$-$C_{10}$ alkylene) halogen, $SO_2(C_1$-$C_{10}$ alkyl), $SO_2(C_1$-$C_{10}$ alkylene)-$CF_3$, $SO_2(C_1$-$C_{10}$ alkylene)$OCH_3$, $SO_2(C_1$-$C_{10}$ alkylene) halogen, $C(O)(C_1$-$C_{10}$ alkyl), $C(O)(C_1$-$C_{10}$ alkylene)$CF_3$, $C(O)(C_1$-$C_{10}$ alkylene)$OCH_3$, $C(O)(C_1$-$C_{10}$ alkylene) halogen, $C(O)NH(C_1$-$C_{10}$ alkyl), $C(O)N(C_1$-$C_{10}$ alkyl)$_2$, $(C_1$-$C_{10}$ alkyl)$C(O)OH$, $C(O)NH_2$, or oxetane.

3. The pharmaceutical composition of claim 1, wherein A has the structure




wherein:

n is 0;

$R^3$ is H, $C_1$-$C_4$ alkyl, or oxetane;

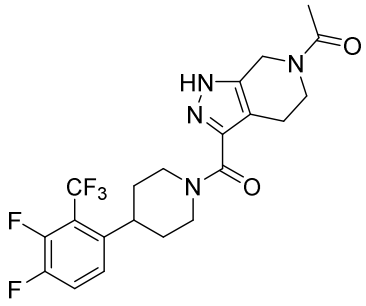
$Y_1$ and $Y_3$ are each $CH_2$ or $C(CH_3)_2$;

$Y_2$ is O, $SO_2$, or $NR^6$; and

$R^6$ is H, $C_1$-$C_4$ alkyl, $C_3$-$C_6$ cycloalkyl, $(C_1$-$C_4$ alkylene)$CF_3$, $(C_1$-$C_4$ alkylene)$OCH_3$, $(C_1$-$C_4$ alkylene) halogen, $SO_2(C_1$-$C_4$ alkyl), $SO_2(C_1$-$C_4$ alkylene)$CF_3$, $SO_2(C_1$-$C_4$ alkylene)$OCH_3$, $SO_2(C_1$-$C_4$ alkylene) halogen, $C(O)(C_1$-$C_4$ alkyl), $C(O)(C_1$-

~~$C_4$-alkylene)$CF_3$, C(O)($C_1$-$C_4$-alkylene)$OCH_3$, C(O)($C_1$-$C_4$-alkylene)-halogen, C(O)NH($C_1$-$C_4$-alkyl), C(O)N($C_1$-$C_4$-alkyl)$_2$, ($C_1$-$C_4$-alkylene)C(O)OH, C(O)$NH_2$, or oxetane.~~

~~4.~~2. The pharmaceutical composition of claim 1, wherein the compound of Formula (I) has the structure:




, or a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof.

~~5.~~3. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) is effective to reduce RBP4 concentrations in dosages forms of 1 to 200mg or 5 to 25mg.

~~6. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) is a micronized crystalline.~~

~~7. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) is a polymorph exhibiting an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.~~

~~8.~~4. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) is amorphous and molecularly dispersed in the dispersion polymer~~;~~ selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, and combinations thereof.

~~9. The pharmaceutical composition of any one of the preceding claims, wherein the dispersion polymer is selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, and combinations thereof.~~

~~10. The pharmaceutical composition of any one of the preceding claims, wherein the dispersion polymer comprises HPMC.~~

~~11. The pharmaceutical composition of any one of claims 1-6, wherein the dispersion polymer comprises HPMC-AS.~~

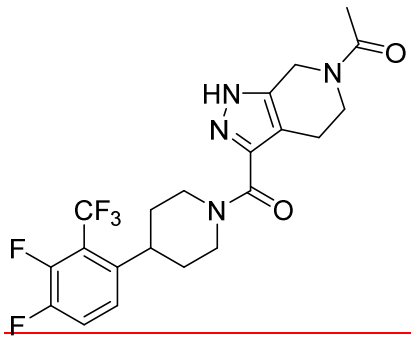
~~12.~~5. The pharmaceutical composition of any one of the preceding claims, wherein the dispersion polymer comprises about 1-99% by weight, 20-80% by weight, or 40-60% by weight of the solid dispersion.

~~13. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) comprises about 1-99% by weight, about 20-80% by weight, or about 40-60% by weight of the solid dispersion.~~

~~14.~~6. The pharmaceutical composition of any one of the preceding claims, wherein the ratio of the compound of Formula (I):dispersion polymer is about 20:80 (w/w) or about 40:60 (w/w) in the solid dispersion.

~~15. The pharmaceutical composition of any one of the preceding claims, wherein the ratio of the compound of Formula (I):dispersion polymer is about 40:60 (w/w) in the solid dispersion.~~

~~16. The pharmaceutical composition of claim 14 or 15, wherein the compound of Formula (I) is~~



~~and the dispersion polymer is HPMC-AS.~~

~~17.~~7. The pharmaceutical composition of claim 5 or 6~~any one of claims 10-16~~, wherein the dispersion polymer is HPMC-AS having an acetyl content from 7-11 wt%, a succinyl content from 10-14 wt%, a methoxyl content from 21-25 wt%, and a hydroxypropyl content from 5-9 wt%.

~~18. The pharmaceutical composition of any one of claims 10-16, wherein the dispersion polymer is HPMC-AS having an acetyl content from 10-14 wt%, a succinyl content from 4-8 wt%, a methoxyl content from 22-26 wt%, and a hydroxypropyl content from 6-10 wt%.~~

~~19.~~8. The pharmaceutical composition of any one of claims 1-~~7~~9, wherein the dispersion polymer comprises polyvinylpyrrolidone (PVP); wherein the PVP is present in a ratio with the compound of Formula (I) from about 10:1 to about 1:1.~~-~~

~~20. The pharmaceutical composition of claim 19, wherein the PVP is present in a ratio with the compound of Formula (I) from about 10:1 to about 1:1.~~

~~21. The pharmaceutical composition of claim 19 or 20, wherein the PVP is a present in a ratio with the compound of Formula (I) of about 2:1, about 3:1, or about 5:1.~~

~~22.~~9. The pharmaceutical composition of claim 8~~any one of claims 19-21~~, wherein the PVP has a molecular weight average molecular weight from about 7,000 Daltons to about 11,000 Daltons.

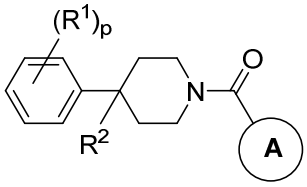
~~23. The pharmaceutical composition of any one of the preceding claims, further comprising a filler, a sweetener, a disintegrant, a wetting agent, a glidant, a lubricant, or a surfactant, or any combinations thereof.~~

~~24. The pharmaceutical composition of any one of the preceding claims, wherein the solid dispersion further comprises a filler, a sweetener, a disintegrant, a wetting agent, a glidant, a lubricant, or a surfactant, or any combinations thereof.~~

~~25. The pharmaceutical composition of any one of the preceding claims, wherein the solid dispersion has an average particle size of less than 10 µm or less than 20 µm.~~

~~26.~~10. A nanosuspension pharmaceutical composition comprising:

a compound of Formula (I), a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:




Formula (I)

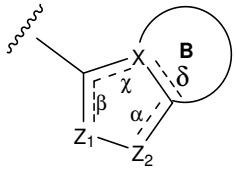
wherein:

each $R^1$ is independently halogen, haloalkyl, or alkyl;

$R^2$ is -H, -OH, or halogen;

p is 0, 1, 2, 3, 4, or 5;

**A** has the structure:




wherein:

α, β, χ, and δ are each independently absent or present, and when present each is a bond;

X is C;

$Z_1$ is S, O, or N;

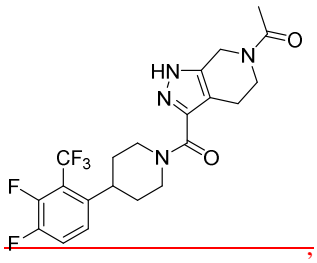
$Z_2$ is S, O, N, or $NR^3$;

$R^3$ is H, $C_1$-$C_4$ alkyl, or oxetane; and

B is a substituted or unsubstituted fused 5-, 6-, or 7- membered ring structure;

wherein the compound of Formula (I) is suspended in a pharmaceutically acceptable solvent.

~~27. The nanosuspension pharmaceutical composition of claim 26, wherein the compound of Formula (I) is~~




~~, or a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof.~~

~~28. The nanosuspension pharmaceutical composition of claim 27, wherein the compound of Formula (I) is a polymorph exhibiting an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.~~

~~29.~~11. The nanosuspension pharmaceutical formulation of claim 10~~any one of claims 26-28~~, wherein the concentration of the compound of Formula (I) is from about 1 mg/mL to about 50 mg/mL.

~~30.~~12. The nanosuspension pharmaceutical formulation of claim 10 or 11~~any one of claims 26-29~~, wherein the compound of Formula (I) is micronized.

~~31.~~13. The nanosuspension pharmaceutical formulation of any one of claims 10-12~~26-30~~, wherein the compound of Formula (I) has an average particle size of less than 1000 nm.

~~32.~~14. The nanosuspension pharmaceutical formulation of any one of claims 10-13~~26-31~~, further comprising a surfactant, wherein the surfactant comprises sodium dodecyl sulfate, a poloxamer, or a polysorbate.~~.~~

~~33.~~15. The nanosuspension pharmaceutical formulation of claim 14~~32~~, wherein the surfacing is present at a concentration from about 0.01% to about 1%.

~~34. The nanosuspension pharmaceutical formulation of claim 32 or 33, wherein the surfactant comprises sodium dodecyl sulfate, a poloxamer, or a polysorbate.~~

~~35.~~16. The nanosuspension pharmaceutical formulation of any one of claims 10-15~~26-34~~, further comprising an excipient, wherein the excipient comprises hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, or any combinations thereof.~~.~~

~~36. The nanosuspension pharmaceutical formulation of claim 35, wherein the excipient comprises hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl~~

~~alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, or any combinations thereof.~~

~~37~~17. The nanosuspension pharmaceutical composition of claim 16~~35 or 36~~, wherein the excipient is present at a concentration from about 0.1% to about 5%.

~~38. The pharmaceutical composition of any one of claims 1-25, wherein the pharmaceutical composition is in the form of a tablet.~~

~~39. The pharmaceutical composition of any one of claims 1-38, wherein the pharmaceutical composition is in the form of a capsule.~~

~~40. A method of treating an eye disease comprising administering a therapeutically effective amount of a pharmaceutical composition of any one of the preceding claims to a subject in need thereof.~~

~~41. The method of claim 40, wherein the eye disease is a disease characterized by excessive lipofuscin accumulation in the retina.~~

~~42. The method of claim 41, wherein the disease characterized by excessive lipofuscin accumulation is Age-Related Macular Degeneration, dry (atrophic) Age-Related Macular Degeneration, Juvenile Macular Degeneration (Stargardt Disease), Best disease, adult vitelliform maculopathy, Geographic Atrophy, Stargardt-like macular dystrophy, diabetic retinopathy, or an ABCA4 gene associated retinal disease.~~

~~43. A method for lowering the serum concentration of RBP4 in a subject, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition of any one of claims 1-35.~~

~~44. The method of any one of claims 40-43, wherein the therapeutically effective amount of the pharmaceutical composition comprises about 0.1 mg to about 400 mg of the compound of Formula (I).~~

~~45. The method of any one of claims 40-44, wherein the therapeutically effective amount of the pharmaceutical composition comprises about 0.5 mg to about 50 mg of the compound of Formula (I).~~

~~46. The method of any one of claims 40-45, wherein the therapeutically effective amount of the pharmaceutical composition comprises about 0.1 mg, about 0.5 mg, about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, or about 400 mg of the compound of Formula (I).~~

47. The method of any one of claims 40-46, wherein the pharmaceutical composition is administered one, two, three, or four times daily.

48. The method of any one of claims 40-46, wherein the pharmaceutical composition is administered daily, every other day, every other day 3 times a week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 3 days, every 4 days, every 5 days, every 6 days, weekly, bi-weekly, 3 times a week, 4 times a week, 5 times a week, 6 times a week, once a month, twice a month, 3 times a month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, or once every 6 months.

49. The method of any one of claims 40-46, wherein the pharmaceutical composition is administered once daily.

50. The method of any one of claims 40-49, wherein the pharmaceutical composition is administered orally.

51. The method of any one of claims 40-50, wherein the serum RBP4 concentration of the subject is reduced to below 1 μM after treatment.

52. A method of manufacturing a solid dispersion comprising the steps of

(i)(i) adding a solvent to a vessel;

(ii)(ii) adding a compound of Formula (I) of any of claims 1-4 or its pharmaceutically acceptable salt to the vessel;

(iii)(iii) adding a dispersion polymer to the vessel to obtain a first mixture;

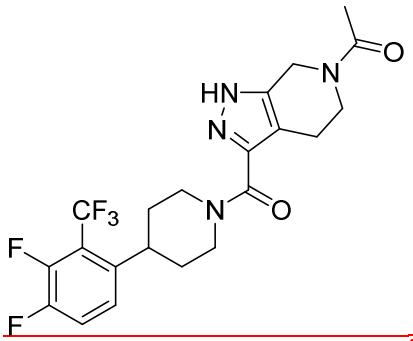
(iv)(iv) mixing the first mixture until the compound of Formula (I) or its pharmaceutically acceptable salt and the dispersion polymer are dissolved in the solvent to obtain a first solution; and

(v)(v) dry spraying the first solution to obtain a first solid.

53. The method of claim 52, wherein the dispersion polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, and combinations thereof.

54. The method of claim 52 or 53, wherein the dispersion polymer is HPMC-AS or polyvinyl pyrrolidine.

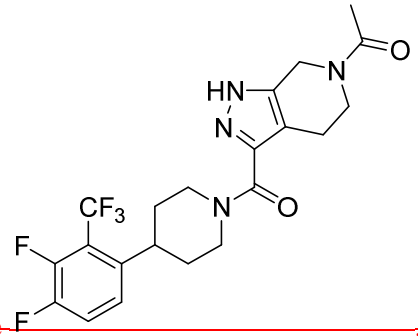
~~55. The method of any of one of claims 52-54, wherein the compound of Formula (I) has the structure:~~



~~, or a pharmaceutically acceptable salt, crystalline solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof.~~

~~56. The method of any one of claims 52-55, wherein the solvent comprises acetic acid, acetone, acetonitrile, benzene, tert-butyl alcohol, tert-butyl methyl ether, carbon tetrachloride, chloroform, cyclohexane, 1,2-dichloroethane, dichloromethane, diethyl ether, diglyme, 1,2, dimethoxyethane, dimethyl acetamide, dimethylformamide, dimethyl sulfoxide, dioxane, ethanol, ethyl acetate, ethyl methyl ketone, ethylene glycol, hexanes, hexamethylphosphoramide, methanol, nitromethane, pentanes, 2-proponal, pyridine, tetrahydrofuran, toluene, xylenes, or any combination thereof.~~

~~57. A method for lowering the serum concentration of RBP4 in a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound having~~



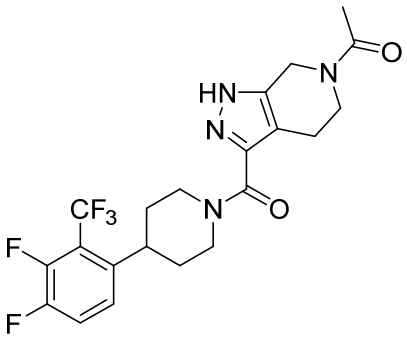
~~the structure~~ ~~, or a pharmaceutically acceptable salt, cystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof;~~

~~wherein the pharmaceutical composition is administered in an amount of about 10 mg;~~

~~wherein the pharmaceutical composition is administered daily;~~

~~wherein the serum or plasma levels of RBP4 of the subject are reduced to below 1 μM.~~

~~58~~18. A polymorph of a compound of Formula (I) having the structure



,

wherein the polymorph exhibits an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.

~~59~~19. The polymorph of claim 18~~54~~, wherein the polymorph is crystalline.

~~60. The polymorph of claim 58 or 59, wherein the polymorph exhibits an x-ray powder diffraction pattern having at least five characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.~~

~~61. The polymorph of claim 58 or 59, wherein the polymorph exhibits an x-ray powder diffraction pattern having characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.~~

~~62. The polymorph of any one of claims 58-61, wherein the polymorph is micronized.~~

~~63~~20. The polymorph of any one of claims 18 or 19~~58-62~~, wherein the polymorph has an average particle size of less than 20 µm, less than 10 µm, less than 1 µm, or less than 100 nm.