SUMMARY

[0005] The present disclosure fulfills these needs and others by providing crystalline forms of Compound A, salts, and solvates. The present disclosure also provides an amorphous form of Compound A. The present disclosure also provides pharmaceutical compositions comprising amorphous or one or more crystalline forms of Compound A. The disclosure also provides processes for making the amorphous and crystalline solid forms and methods for using them to treat, and prevent HIF-associated disorders including conditions involving anemia, ischemia, and hypoxia.

[0006] ~~Thus, one embodiment~~In a first aspect, there is provided ~~is~~ a crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (Compound A Form A) characterized by an X-ray powder diffractogram comprising the following peaks: 8.5, 16.2, and 27.4 °2θ ± 0.2 °2θ.

[0007] ~~Another embodiment~~ In a second aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid hemihydrate (Compound A Form B) characterized by an X-ray powder diffractogram comprising the following peaks: 4.2, 8.3, and 16.6 °2θ ± 0.2 °2θ.

[0008] ~~Yet another embodiment~~In a third aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid hexafluoropropan-2-ol solvate (Compound A Form C) characterized by an X-ray powder diffractogram comprising the following peaks: 4.5, 13.7, and 16.4 °2θ ± 0.2 °2θ.

[0009] ~~Yet another embodiment~~In a fourth aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid DMSO:water solvate (Compound A Form D) characterized by an X-ray powder diffractogram comprising the following peaks: 8.4, 8.5, and 16.8 °2θ ± 0.2 °2θ.

[0010] ~~Yet another embodiment~~In a fifth aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid sodium salt (Compound A sodium salt) characterized by an X-ray powder diffractogram comprising the following peaks: 5.3, 16.0, and 21.6 °2θ ± 0.2 °2θ.

[0011] ~~Yet another embodiment~~In a sixth aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid L-arginine salt (Compound A L-arginine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 20.8, 21.8, and 25.4 °2θ ± 0.2 °2θ.

[00010012] ~~Yet another embodiment~~In a seventh aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid L-lysine salt (Compound A L-lysine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 19.8, 20.7, and 21.2 °2θ ± 0.2 °2θ.

[0013] ~~Yet another embodiment~~ In an eighth aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid ethanolamine salt (Compound A ethanolamine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 21.8, 22.7, and 27.1 °2θ ± 0.2 °2θ.

[0014] ~~Yet another embodiment~~ In a ninth aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid diethanolamine salt (Compound A diethanolamine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 16.9, 23.7, and 25.0 °2θ ± 0.2 °2θ.

[0015] ~~Yet another embodiment~~In a tenth aspect, there is provided ~~a~~is crystalline [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid tromethamine salt (Compound A tromethamine salt) characterized by an X-ray powder diffractogram comprising the following peaks: 10.1, 14.2, and 21.1 °2θ ± 0.2 °2θ.

[0016] ~~Yet another embodiment~~In an eleventh aspect, there is provided ~~an~~is amorphous [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid (amorphous Compound A).

[0017] ~~Yet another embodiment~~In a twelfth aspect, there is provided ~~a~~is substantially amorphous [(4-hydroxy-1-methyl-7-phenoxy-isoquinoline-3-carbonyl)-amino]-acetic acid potassium salt (Compound A potassium salt).

[0018] Still another embodiment provided is directed to a pharmaceutical composition comprising a crystalline or amorphous form of Compound A, or a salt thereof, and a pharmaceutically acceptable excipient.

[0018a] In a thirteenth aspect, there is provided a pharmaceutical composition comprising a compound selected from the group consisting of: Compound A Form A as defined above, Compound A Form B as defined above, Compound A Form C as defined above, Compound A Form D as defined above, Compound A sodium salt as defined above, Compound A L-arginine salt as defined above, Compound A L-lysine salt as defined above, Compound A ethanolamine salt as defined above, Compound A diethanolamine salt as defined above, Compound A tromethamine salt as defined above, amorphous Compound A as defined above, and Compound A potassium salt as defined above, and a pharmaceutically acceptable excipient.

[0019] Additionally, the disclosure provides in one embodiment a method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF). The method comprises administering to a patient in need thereof a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt, Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0020] Also provided is a method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO), comprising administering to a patient in need thereof, a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt, Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0021] Also provided is a method for treating, pretreating, or delaying onset or progression of anemia, comprising administering to a patient in need thereof, a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt, Compound A L-arginine salt,

Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0022] Also provided is a method of inhibiting the activity of a HIF hydroxylase enzyme, the method comprising bringing into contact the HIF hydroxylase enzyme and a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A, Compound A Form B, Compound A Form C, Compound A Form D, Compound A sodium salt,

Compound A L-arginine salt, Compound A L-lysine salt, Compound A ethanolamine salt, Compound A diethanolamine salt, Compound A tromethamine salt, amorphous Compound A, and Compound A potassium salt, as described generally above.

[0022a] In a fourteenth aspect, there is provided the use of a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A as defined above, Compound A Form B as defined above, Compound A Form C as defined above, Compound A Form D as defined above, Compound A sodium salt as defined above, Compound A L-arginine salt as defined above, Compound A L-lysine salt as defined above, Compound A ethanolamine salt as defined above, Compound A diethanolamine salt as defined above, Compound A tromethamine salt as defined above, amorphous Compound A as defined above, and Compound A potassium salt as defined above, for the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF).

[0022b] In a fifteenth aspect, there is provided the use of a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A as defined above, Compound A Form B as defined above, Compound A Form C as defined above, Compound A Form D as defined above, Compound A sodium salt as defined above, Compound A L-arginine salt as defined above, Compound A L-lysine salt as defined above, Compound A ethanolamine salt as defined above, Compound A diethanolamine salt as defined above, Compound A tromethamine salt as defined above, amorphous Compound A as defined above, and Compound A potassium salt as defined above, for the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO).

[0022c] In a sixteenth aspect, there is provided the use of a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A as defined above, Compound A Form B as defined above, Compound A Form C as defined above, Compound A Form D as defined above, Compound A sodium salt as defined above, Compound A L-arginine salt as defined above, Compound A L-lysine salt as defined above, Compound A ethanolamine salt as defined above, Compound A diethanolamine salt as defined above, Compound A tromethamine salt as defined above, amorphous Compound A as defined above, and Compound A potassium salt as defined above, for the manufacture of a medicament for treating, pretreating, or delaying onset or progression of anemia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **FIG. 1** is an X-ray powder diffraction pattern of Compound A Form A.

[0024] **FIG. 2** is a differential scanning calorimetry (DSC) curve of Compound A Form A.

[0025] **FIG. 3** is an X-ray powder diffraction pattern of Compound A Form B (bottom) plotted with an X-ray powder diffraction pattern of Compound A Form A (top).

[0026] **FIG. 4** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A Form B.

[0027] **FIG. 5** is an X-ray powder diffraction pattern of Compound A Form C (bottom) plotted with an X-ray powder diffraction pattern of Compound A Form A (top).

[0028] **FIG. 6** is a differential scanning calorimetry (DSC) curve (top) and a thermogravimetric analysis (TGA) (bottom) of Compound A Form C.

[0029] **FIG. 7** is an X-ray powder diffraction pattern of Compound A Form D.

[0030] **FIG. 8** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A Form D.

[0031] **FIG. 9** is an X-ray powder diffraction pattern of Compound A sodium salt as isolated (bottom) and at 40 °C/75% RH (top).

[0032] **FIG. 10** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A sodium salt.

[0033] **FIG. 11** is an X-ray powder diffraction pattern of Compound A L-arginine salt as isolated (bottom) and at 40 °C/75% RH (top).

[0034] **FIG. 12** is a thermogravimetric analysis (TGA) (top) and a differential scanning calorimetry (DSC) curve (bottom) of Compound A L-arginine salt.

[0035] **FIG. 13** is an X-ray powder diffraction pattern of Compound A L-lysine salt as isolated (bottom) and at 40 °C/75% RH (top).

claim 6, Compound A Form C according to claim 11, Compound A Form D according to claim 16, Compound A sodium salt according to claim 21, Compound A L-arginine salt according to claim 26, Compound A L-lysine salt according to claim 31, Compound A ethanolamine salt according to claim 36, Compound A diethanolamine salt according to claim 41, Compound A tromethamine salt according to claim 46, amorphous Compound A according to claim 51, and Compound A potassium salt according to claim 52, and a pharmaceutically acceptable excipient.

56. The pharmaceutical composition of claim 55, comprising Compound A in Form A.

57. The pharmaceutical composition of claim 56, wherein at least about 85% of Compound A is in Form A.

58. The pharmaceutical composition of claim 56, wherein at least about 90% of Compound A is in Form A.

59. The pharmaceutical composition of claim 56, wherein at least about 95% of Compound A is in Form A.

60. The pharmaceutical composition of claim 56, wherein at least about 99% of Compound A is in Form A.

61. The pharmaceutical composition of claim 56, wherein at least about 99.5% of Compound A is in Form A.

62. The pharmaceutical composition of claim 56, wherein at least about 99.9% of Compound A is in Form A.

63. The pharmaceutical composition of claim 56, wherein at least about 99.99% of Compound A is in Form A.

64. ~~A method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF), comprising administering to a patient in need thereof,~~ Use of a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A according to claim 1, Compound A Form B according to claim 6, Compound A Form C according to claim 11, Compound A Form D according to claim

16, Compound A sodium salt according to claim 21, Compound A L-arginine salt according to claim 26, Compound A L-lysine salt according to claim 31, Compound A ethanolamine salt according to claim 36, Compound A diethanolamine salt according to claim 41, Compound A tromethamine salt according to claim 46, amorphous Compound A according to claim 51, and Compound A potassium salt according to claim 52, for the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by hypoxia inducible factor (HIF).

65. The use~~method~~ of claim 64, wherein the condition mediated at least in part by HIF is tissue damage associated with ischemia or hypoxia.

66. The use~~method~~ of claim 65, wherein the ischemia is associated with an acute event selected from the group consisting of myocardial infarction, pulmonary embolism, intestinal infarction, chronic kidney failure, ischemic stroke, and renal ischemic-reperfusion injury.

67. The use~~method~~ of claim 65, wherein the ischemia is associated with a chronic event selected from the group consisting of cardiac cirrhosis, transient ischemic attack, macular degeneration, peripheral artery disease, and congestive heart failure.

68. ~~A method for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO), comprising administering to a patient in need thereof,~~ Use of a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A according to claim 1, Compound A Form B according to claim 6, Compound A Form C according to claim 11, Compound A Form D according to claim 16, Compound A sodium salt according to claim 21, Compound A L-arginine salt according to claim 26, Compound A L-lysine salt according to claim 31, Compound A ethanolamine salt according to claim 36, Compound A diethanolamine salt according to claim 41, Compound A tromethamine salt according to claim 46, amorphous Compound A according to claim 51, and Compound A potassium salt according to claim 52, for the manufacture of a medicament for treating, pretreating, or delaying onset or progression of a condition mediated at least in part by erythropoietin (EPO).

69. ~~A method for treating, pretreating, or delaying onset or progression of anemia, comprising administering to a patient in need thereof,~~ Use of a therapeutically effective amount of a compound selected from the group consisting of: Compound A Form A according to claim 1, Compound A Form B according to claim 6, Compound A Form C according to claim 11, Compound A Form D according to claim 16, Compound A sodium salt according to claim 21,

Compound A L-arginine salt according to claim 26, Compound A L-lysine salt according to claim 31, Compound A ethanolamine salt according to claim 36, Compound A diethanolamine salt according to claim 41, Compound A tromethamine salt according to claim 46, amorphous Compound A according to claim 51, and Compound A potassium salt according to claim 52, for the manufacture of a medicament for treating, pretreating, or delaying onset or progression of anemia.

70. The ~~method~~ use of claim 64, 68 or 69, wherein the compound used in the method is Compound A Form A.

71. The use~~method~~ of claim 64, 68 or 69, wherein at least about 85% of the compound used in the method is Compound A Form A.

72. The use~~method~~ of claim 64, 68 or 69, wherein at least about 90% of the compound used in the method is Compound A Form A.

73. The use~~method~~ of claim 64, 68 or 69, wherein at least about 95% of the compound used in the method is Compound A Form A.

74. The use~~method~~ of claim 64, 68 or 69, wherein at least about 99% of the compound used in the method is Compound A Form A.

75. The use~~method~~ of claim 64, 68 or 69, wherein at least about 99.5% of the compound used in the method is Compound A Form A.

76. The use~~method~~ of claim 64, 68 or 69, wherein at least about 99.9% of the compound used in the method is Compound A Form A.

77. The use~~method~~ of claim 64, 68 or 69, wherein at least about 99.99% of the compound is Compound A Form A.