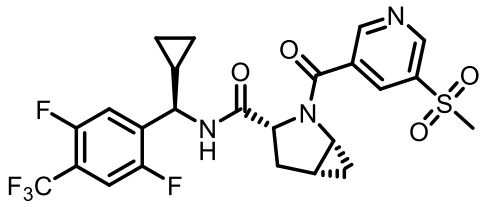
POLYMORPHS AND COCRYSTALS OF A CARDIAC TROPONIN ACTIVATOR

BACKGROUND

[0001] The compound (1R,3R,5R)-N-((R)-cyclopropyl(2,5-difluoro-4-(trifluoromethyl)phenyl)methyl)-2-(5-(methylsulfonyl)nicotinoyl)-2-azabicyclo[3.1.0]hexane-3-carboxamide, is useful as a cardiac troponin activator:

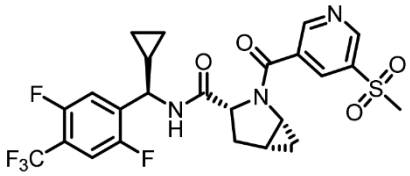


("Compound A").

[0002] There is a need for various new salt and crystalline forms of Compound A with different chemical and physical stabilities, and formulations and uses of the same.

SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a free base anhydrous crystalline form of Compound A ("Form I"), wherein Compound A is:



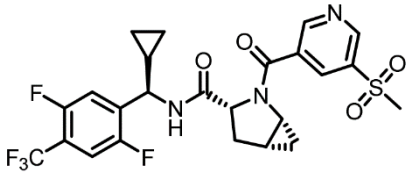
("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 9.78, 12.45, 15.70, 16.46, and 16.94 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 8.23, 24.40, 25.03, 25.49, and 32.03 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 19.56, 20.11, 22.99, 23.97, 29.53, 41.91, and 42.83 ± 0.2° 2θ using Cu Kα radiation.

[0002b] In another aspect of the present disclosure, there is provided a free base anhydrous crystalline form of Compound A ("Form II"), wherein Compound A is:

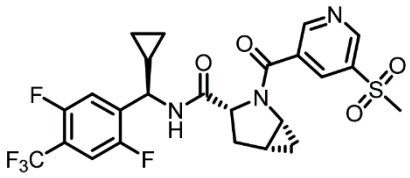


("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 7.67, 11.54, 18.27, and 23.28 ± 0.2° 2θ using Cu Kα radiation;

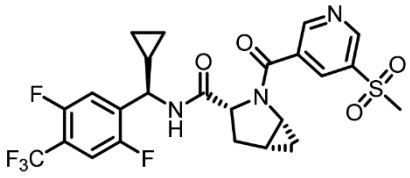
optionally further characterized by XRPD pattern peaks at 15.36, 16.33, 18.58, 21.38, 23.59, 24.61, 27.09, 43.40, and 44.26 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 18.01, 25.17, 38.15, and 39.26 ± 0.2° 2θ using Cu Kα radiation.

[0002c] In a further aspect of the present disclosure, there is provided a free base monohydrate crystalline form of Compound A ("Form III"), wherein Compound A is:


("Compound A"),

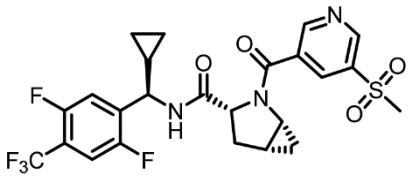
characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 7.31, 10.77, and 13.96 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 16.60, 18.56, 18.84, 19.41, 20.57, 21.61, 21.92, 22.28, 23.34, 24.23, 24.70, 25.69, and 28.87 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 7.94, 20.10, 23.88, and 28.38 ± 0.2° 2θ using Cu Kα radiation.

[0002d] In another aspect of the present disclosure, there is provided a free base anhydrous crystalline form of Compound A ("Form IV"), wherein Compound A is:


("Compound A"),

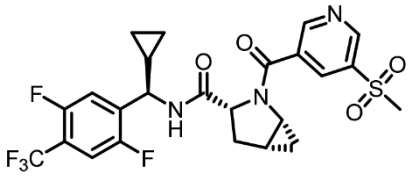
characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.06, 11.29, and 14.97 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 17.19, 17.63, 18.39, 18.95, 19.17, 20.50, 24.87, 26.03, 26.62, 27.99, and 29.25 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 12.08, 20.17, 22.37, 22.86, 25.69, 28.26, and 28.73 ± 0.2° 2θ using Cu Kα radiation.

[0002e] In a further aspect of the present disclosure, there is provided a crystalline form of Compound A hydrochloride salt, wherein Compound A is:


("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.45, 16.93, 23.74, 24.59, and 26.57 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 17.33, 17.76, 18.75, 19.51, 19.81, 20.53, 21.36, 22.95, 25.28, 25.89, 26.94, 27.44, and 29.41 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 8.74, 16.08, 19.81, and 28.58 ± 0.2° 2θ using Cu Kα radiation.

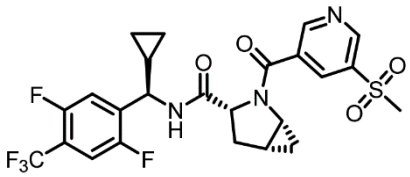
[0002f]In another aspect of the present disclosure, there is provided a crystalline form of Compound A and dichloromethane, wherein Compound A is:



(“Compound A”),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 11.46, 16.91, 23.10, and 24.58 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 8.25, 16.26, 18.82, 19.50, 19.90, 20.52, 20.79, 21.58, 23.92, and 29.35 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 6.76, 25.18, 26.20, 26.95, 27.18, 27.62, and 28.26 ± 0.2° 2θ using Cu Kα radiation.

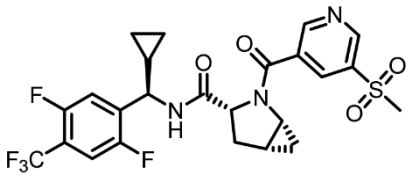
[0002g] In a further aspect of the present disclosure, there is provided a crystalline form of Compound A and nitromethane, wherein Compound A is:



(“Compound A”),

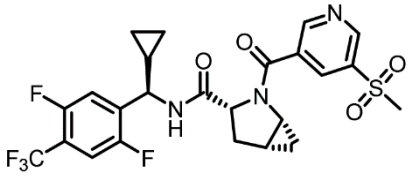
characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.94, 15.86, 17.12, 19.51, 19.83, and 24.41 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 10.18, 18.16, 20.54, 21.93, 23.06, 23.92, and 25.37 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 19.01, 22.68, 26.61, and 28.32 ± 0.2° 2θ using Cu Kα radiation.

[0002h] In another aspect of the present disclosure, there is provided a crystalline form of Compound A and hexafluoro-2-propanol, wherein Compound A is:


(“Compound A”),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 16.17, 16.70, 18.20, and 23.03 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 9.49, 11.20, 20.18, 21.39 23.74, 25.46, 27.00, 29.24, and 33.76 ± 0.2° 2θ using Cu Kα radiation.

[0002i] In a further aspect of the present disclosure, there is provided a cocrystal comprising Compound A


(Compound A)

and a coformer, wherein the coformer comprises propyl gallate, glycerol, propylene glycol, maltol, urea, or a mixture thereof.

[0002j] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the crystalline form or cocrystal of Compound A disclosed herein and a pharmaceutically acceptable carrier.

[0002k] In a further aspect of the present disclosure, there is provided a use of a crystalline form or cocrystal of Compound A disclosed herein, or the composition disclosed herein, in the manufacture of a medicament for treating heart failure.

[0002l] In another aspect of the present disclosure, there is provided a crystalline form or cocrystal of Compound A disclosed herein, or the composition disclosed herein, for use in treating heart failure.

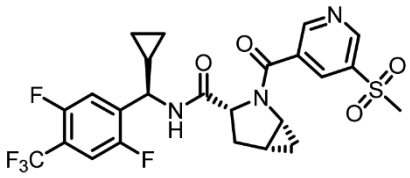
[0003] Provided herein are crystalline forms of Compound A or a salt thereof, including free base crystalline forms, crystalline salts, and crystalline solvates. In some examples, provided herein is the free base anhydrous crystalline Form I of Compound A. In some examples, provided herein is the free base anhydrous crystalline Form II of Compound A. In some examples, provided herein is the free base monohydrate crystalline Form III of Compound A. In some examples, provided herein is the free base anhydrous crystalline Form IV of Compound A. In some examples, provided herein is the crystalline form of Compound A hydrochloride salt. In some examples, provided herein is the crystalline form of Compound A and dichloromethane. In some examples, provided herein is the crystalline form of Compound A and nitromethane. In some examples, provided herein is the crystalline form of Compound A and hexafluoro-2-propanol.

[0004] Also provided herein are cocrystals comprising Compound A and a coformer. In some examples, the coformer comprises propyl gallate. In some examples, the coformer comprises glycerol. In some examples, the coformer comprises propylene glycol. In some examples, the coformer comprises maltol. In some examples, the coformer comprises urea.

[0005] Further provided are pharmaceutical compositions comprising a crystalline form or cocrystal of Compound A or salt thereof as disclosed herein and a pharmaceutical acceptable carrier.

What is Claimed:

1. A free base anhydrous crystalline form of Compound A ("Form I"), wherein Compound A is:



("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 9.78, 12.45, 15.70, 16.46, and 16.94 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 8.23, 24.40, 25.03, 25.49, and 32.03 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 19.56, 20.11, 22.99, 23.97, 29.53, 41.91, and 42.83 ± 0.2° 2θ using Cu Kα radiation.

2. The crystalline form of claim 1, having one or more of the following:

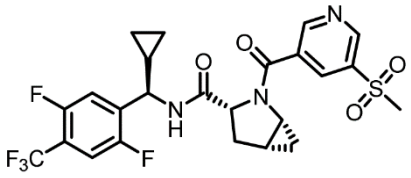
a) an XRPD pattern substantially as shown in Figure 1;

b) an endothermic transition at 147 °C to 157 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 152 °C ± 3°C;

c) a dynamic vapor sorption ("DVS") substantially as shown in Figure 4; and/or

d) a thermogravimetric analysis ("TGA") substantially as shown in Figure 3.

3. A free base anhydrous crystalline form of Compound A ("Form II"), wherein Compound A is:



("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 7.67, 11.54, 18.27, and 23.28 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 15.36, 16.33, 18.58, 21.38, 23.59, 24.61, 27.09, 43.40, and 44.26 ± 0.2° 2θ using Cu Kα radiation;

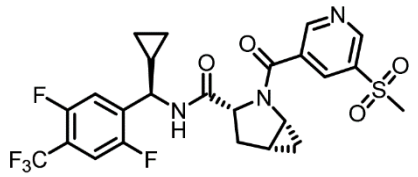
optionally further characterized by XRPD pattern peaks at 18.01, 25.17, 38.15, and 39.26 ± 0.2° 2θ using Cu Kα radiation.

4. The crystalline form of claim 3, having one or more of the following:

a) an XRPD pattern substantially as shown in Figure 5; and/or

b) an endothermic transition at 175 °C to 185 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 181 °C ± 3°C.

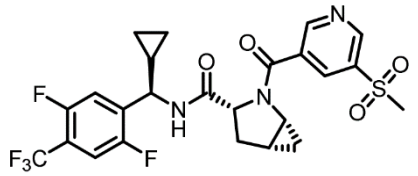
5. A free base monohydrate crystalline form of Compound A ("Form III"), wherein Compound A is:


("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 7.31, 10.77, and 13.96 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 16.60, 18.56, 18.84, 19.41, 20.57, 21.61, 21.92, 22.28, 23.34, 24.23, 24.70, 25.69, and 28.87 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 7.94, 20.10, 23.88, and 28.38 ± 0.2° 2θ using Cu Kα radiation.

6. The crystalline form of claim 5, having one or more of the following:
a) an XRPD pattern substantially as shown in Figure 6;
b) an endothermic transition at 127 °C to 137 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 132 °C ± 3°C;
c) a dynamic vapor sorption ("DVS") substantially as shown in Figure 9; and/or
d) a thermogravimetric analysis ("TGA") substantially as shown in Figure 8.

7. A free base anhydrous crystalline form of Compound A ("Form IV"), wherein Compound A is:

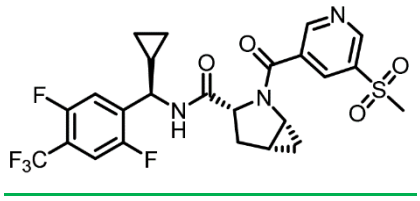

("Compound A"),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.06, 11.29, and 14.97 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 17.19, 17.63, 18.39, 18.95, 19.17, 20.50, 24.87, 26.03, 26.62, 27.99, and 29.25 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 12.08, 20.17, 22.37, 22.86, 25.69, 28.26, and 28.73 ± 0.2° 2θ using Cu Kα radiation.

8. The crystalline form of claim 7, having one or more of the following:
a) an XRPD pattern substantially as shown in Figure 10;
b) an endothermic transition at 160 °C to 175 °C as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 167°C ± 3°C;
c) a dynamic vapor sorption ("DVS") substantially as shown in Figure 13; and/or

d) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 12.

9. A crystalline form of Compound A hydrochloride salt, wherein Compound A is:



(“Compound A”),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.45, 16.93, 23.74, 24.59, and 26.57 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 17.33, 17.76, 18.75, 19.51, 19.81, 20.53, 21.36, 22.95, 25.28, 25.89, 26.94, 27.44, and 29.41 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 8.74, 16.08, 19.81, and 28.58 ± 0.2° 2θ using Cu Kα radiation.

10. The crystalline form of claim 9, having one or more of the following:

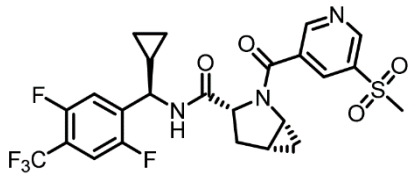
a) an XRPD pattern substantially as shown in Figure 16;

b) an endothermic transition at 125 °C to 140 °C, as measured by differential scanning calorimetry; optionally wherein the endothermic transition is at 134 °C ± 3°C;

c) a dynamic vapor sorption (“DVS”) substantially as shown in Figure 19; and/or

d) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 18.

11. A crystalline form of Compound A and dichloromethane, wherein Compound A is:



(“Compound A”),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 11.46, 16.91, 23.10, and 24.58 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 8.25, 16.26, 18.82, 19.50, 19.90, 20.52, 20.79, 21.58, 23.92, and 29.35 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 6.76, 25.18, 26.20, 26.95, 27.18, 27.62, and 28.26 ± 0.2° 2θ using Cu Kα radiation.

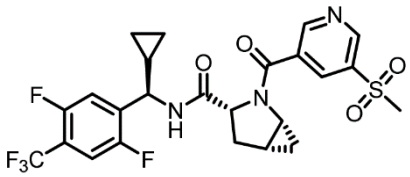
12. The crystalline form of claim 11, having one or more of the following:

a) an XRPD pattern substantially as shown in Figure 20;

b) an endothermic transition at 70 °C to 80 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 76 °C ± 3°C; and/or

c) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 22.

13. A crystalline form of Compound A and nitromethane, wherein Compound A is:


(“Compound A”),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.94, 15.86, 17.12, 19.51, 19.83, and 24.41 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 10.18, 18.16, 20.54, 21.93, 23.06, 23.92, and 25.37 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 19.01, 22.68, 26.61, and 28.32 ± 0.2° 2θ using Cu Kα radiation.

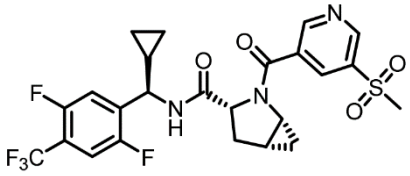
14. The crystalline form of claim 13, having one or more of the following:

a) an XRPD pattern substantially as shown in Figure 23;

b) an endothermic transition at 81°C to 97 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 89 °C ± 3°C; and/or

c) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 25.

15. A crystalline form of Compound A and hexafluoro-2-propanol, wherein Compound A is:


(“Compound A”),

characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 16.17, 16.70, 18.20, and 23.03 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 9.49, 11.20, 20.18, 21.39 23.74, 25.46, 27.00, 29.24, and 33.76 ± 0.2° 2θ using Cu Kα radiation.

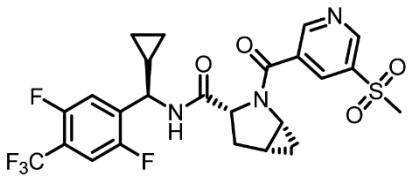
16. The crystalline form of claim 15, having one or more of the following:

a) an XRPD pattern substantially as shown in Figure 26;

b) an endothermic transition at 85 °C to 95 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 90 °C ± 3°C; and/or

c) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 28.

17. A cocrystal comprising Compound A


(Compound A)

and a coformer, wherein the coformer comprises propyl gallate, glycerol, propylene glycol, maltol, urea, or a mixture thereof.

18. The cocrystal of claim 17, wherein the coformer comprises propyl gallate, optionally wherein the cocrystal is characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 8.66, 15.00, 17.72, 18.82, and 20.32 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 9.21, 19.36, 20.49, and 22.57 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 3.05, 11.24, 18.32, 21.73, 22.98, 23.39, 25.01, 25.51, 26.30, 26.52, and 28.31 ± 0.2° 2θ using Cu Kα radiation.

19. The cocrystal of claim 18, having one or more of the following:
a) an XRPD pattern substantially as shown in Figure 29;
b) an endothermic transition at 116 °C to 126 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 121 °C ± 3°C; and/or
c) a thermogravimetric analysis ("TGA") substantially as shown in Figure 31.

20. The cocrystal of claim 17, wherein the coformer comprises glycerol, optionally wherein the cocrystal is characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 16.84, 18.48, 19.40, and 21.49 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 9.70, 15.60, 16.39, 18.95, 22.51, 24.53, and 24.92 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 8.17, 12.38, 22.87, and 27.61 ± 0.2° 2θ using Cu Kα radiation.

21. The cocrystal of claim 20, having one or more of the following:
a) an XRPD pattern substantially as shown in Figure 32;
b) an endothermic transition at 140 °C to 151 °C and 152 °C to 165 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 148 °C ± 3°C and 156 °C ± 3 °C; and/or
c) a thermogravimetric analysis ("TGA") substantially as shown in Figure 34.

22. The cocrystal of claim 17, wherein the coformer comprises propylene glycol, optionally wherein the cocrystal is characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 16.82, 18.26, 18.93, 19.37, and 21.52 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 7.87, 15.61, 16.36, 18.39, 20.39, 21.12, 22.47, and 24.46 ± 0.2° 2θ using Cu Kα radiation;
optionally further characterized by XRPD pattern peaks at 9.69, 20.02, 21.83, 22.85, 23.84, 25.05, and 27.07 ± 0.2° 2θ using Cu Kα radiation.

23. The cocrystal of claim 22, having one or more of the following:
a) an XRPD pattern substantially as shown in Figure 35;
b) a broad dissociation endothermic transition at 80 °C to 135 °C, as measured by differential scanning calorimetry, optionally wherein the broad endothermic transition is at 89 °C to 124 °C ± 3°C; and/or

c) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 37.

24. The cocrystal of claim 17, wherein the coformer comprises maltol, optionally wherein the cocrystal is characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 16.85, 18.18, 19.53, and 23.54 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 6.58, 8.86, 13.68, 14.60, 15.25, 21.52, 25.26, and 26.63 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 4.44, 7.98, and 13.13 ± 0.2° 2θ using Cu Kα radiation.

25. The cocrystal of claim 24, having one or more of the following:

a) an XRPD pattern substantially as shown in Figure 38;

b) a broad dissociation endothermic transition at 125 °C to 135 °C, as measured by differential scanning calorimetry, optionally wherein the broad endothermic transition is at 130 °C ± 3°C; and/or

c) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 40.

26. The cocrystal of claim 17, wherein the coformer comprises urea, optionally wherein the cocrystal is characterized by an X-ray powder diffraction (XRPD) pattern comprising peaks at 3.99, 11.24, 17.62, and 18.37 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 8.01, 8.39, 14.96, 17.47, 18.94, 19.13, 20.51, 24.65, 24.86, 25.70, 25.97, and 26.62 ± 0.2° 2θ using Cu Kα radiation;

optionally further characterized by XRPD pattern peaks at 15.21, 16.93, 17.16, 22.37, 26.35, 28.01, 28.26, 28.77, and 29.25 ± 0.2° 2θ using Cu Kα radiation.

27. The cocrystal of claim 26, having one or more of the following:

a) an XRPD pattern substantially as shown in Figure 41;

b) a dissociation endothermic transition at 160 °C to 170 °C and 171 °C to 180 °C, as measured by differential scanning calorimetry, optionally wherein the endothermic transition is at 167 °C ± 3 °C and 174 °C ± 3 °C; and/or

c) a thermogravimetric analysis (“TGA”) substantially as shown in Figure 43.

28. A pharmaceutical composition comprising the crystalline form or cocrystal of Compound A of any one of claims 1 to 27 and a pharmaceutically acceptable carrier.

29. Use of a crystalline form or cocrystal of Compound A of any one of claims 1 to 27 or the composition of claim 28, in the manufacture of a medicament for treating heart failure.

30. A crystalline form or cocrystal of Compound A of any one of claims 1 to 27 or the composition of claim 28, for use in treating heart failure.