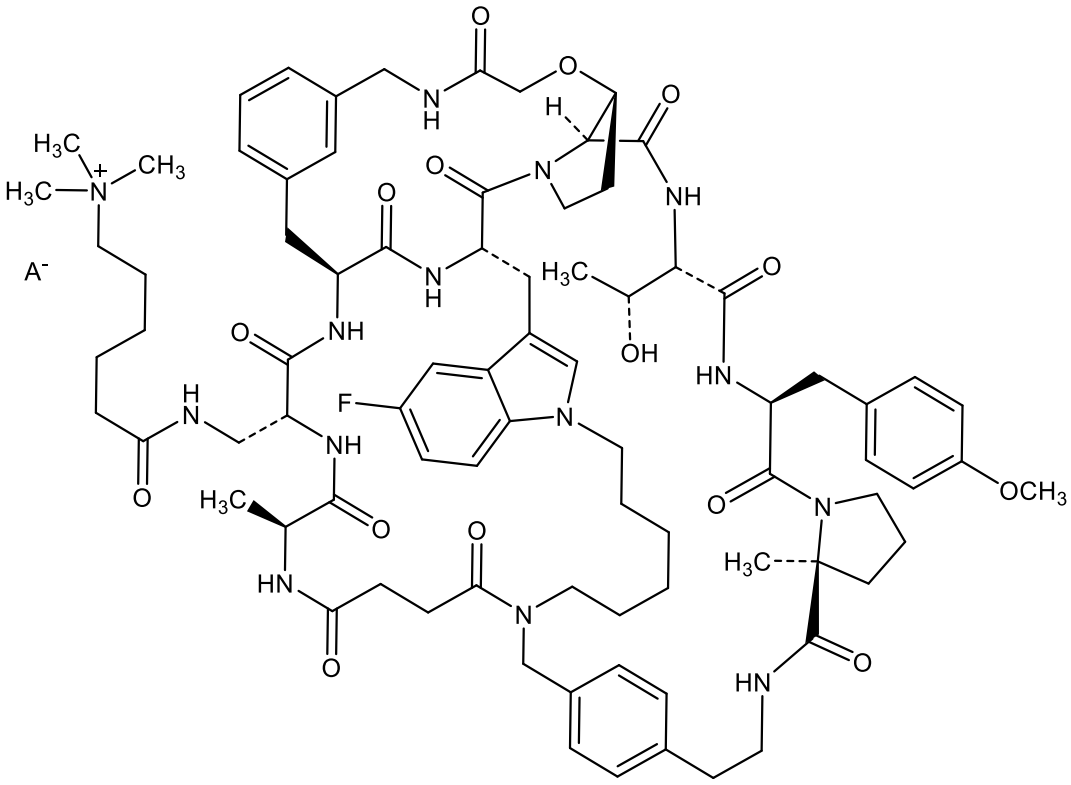
SUMMARY

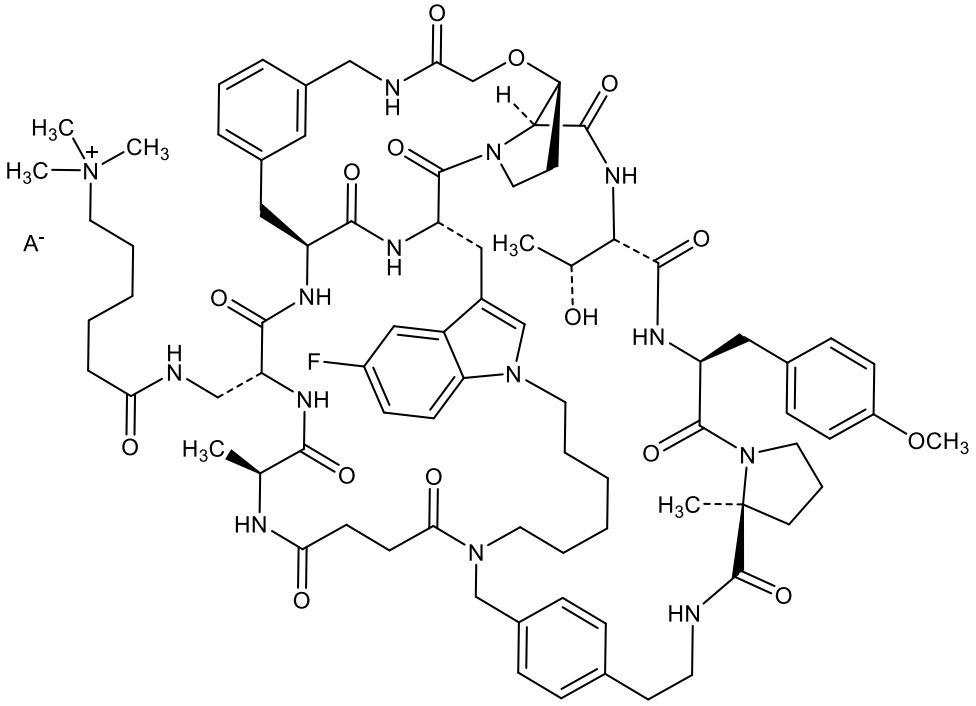
The disclosure relates to a crystalline form of a compound of Formula I:



I

wherein A^- is a pharmaceutically acceptable anion, which has activity as a PCSK9 inhibitor, as well as compositions comprising the same, methods of making the same, and methods of using the same.

In one aspect, there is provided a crystalline form of a compound of Formula I:



I

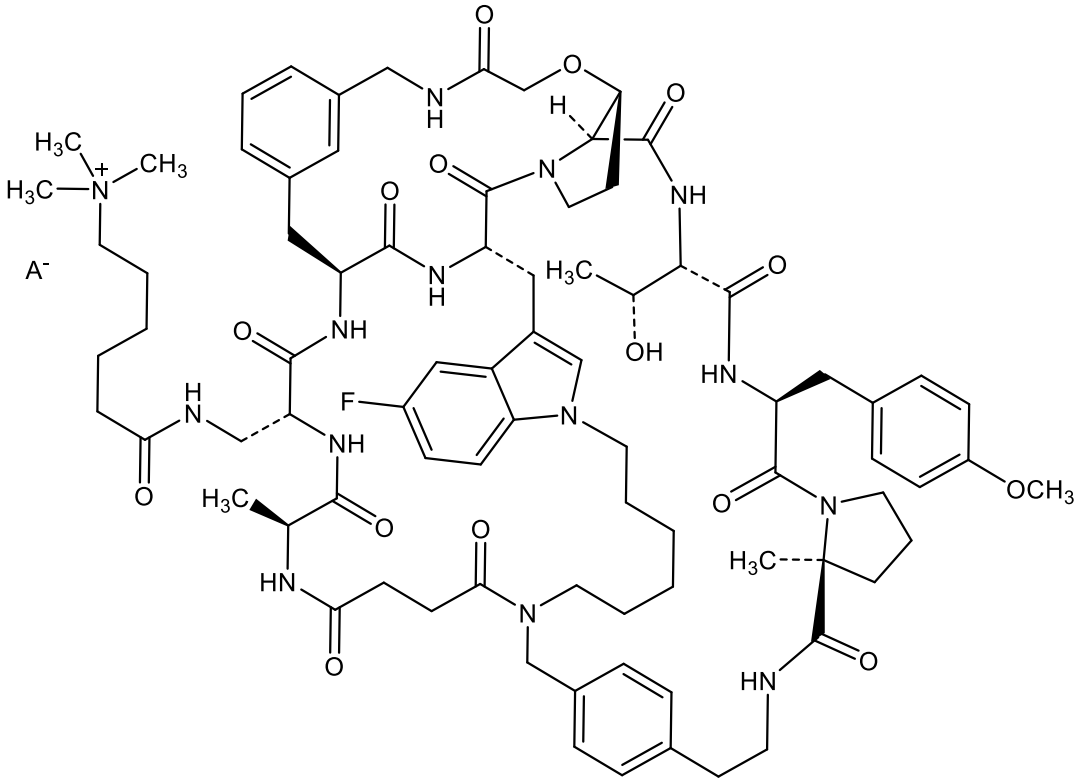
wherein A^- is a pharmaceutically acceptable anion.

In another aspect, there is provided use of the crystalline form as defined herein in the manufacture of a medicament for treating hypercholesterolemia.

In another aspect, there is provided use of the crystalline form as defined herein in the manufacture of a medicament for reducing LDL-C.

In another aspect, there is provided use of the crystalline form as defined herein in the manufacture of a medicament for treating atherosclerotic cardiovascular disease.

In another aspect, there is provided a crystalline form of a compound of Formula I:



I

wherein A^- is a pharmaceutically acceptable anion;

formed by a process comprising adding an alcohol to a starting material,

wherein the starting material is selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, and Compound 6.

In another aspect, there is provided a crystalline form as defined herein for use in inhibiting PCSK9 activity wherein the amount of the crystalline form of the compound of Formula I is from about 5 mg to about 300 mg.

In another aspect, there is provided a pharmaceutical composition, where the pharmaceutical composition comprises the crystalline form as defined herein, wherein the amount of the crystalline form of the compound of Formula I is from about 5 mg to about 300 mg, and the pharmaceutical composition comprises a permeation enhancer.

In another aspect, there is provided use of a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of hypercholesterolemia.

In another aspect, there is provided use of a pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of atherosclerotic cardiovascular disease.

In another aspect, there is provided use of a pharmaceutical composition as defined herein in the manufacture of a medicament for reducing LDL-C.

In another aspect, there is provided a crystalline form as defined herein for use in the treatment of hypercholesterolemia.

In another aspect, there is provided a crystalline form as defined herein for use in the treatment of atherosclerotic cardiovascular disease.

In another aspect, there is provided a crystalline form as defined herein for use in reducing LDL-C.

BRIEF DESCRIPTION OF THE DRAWINGS

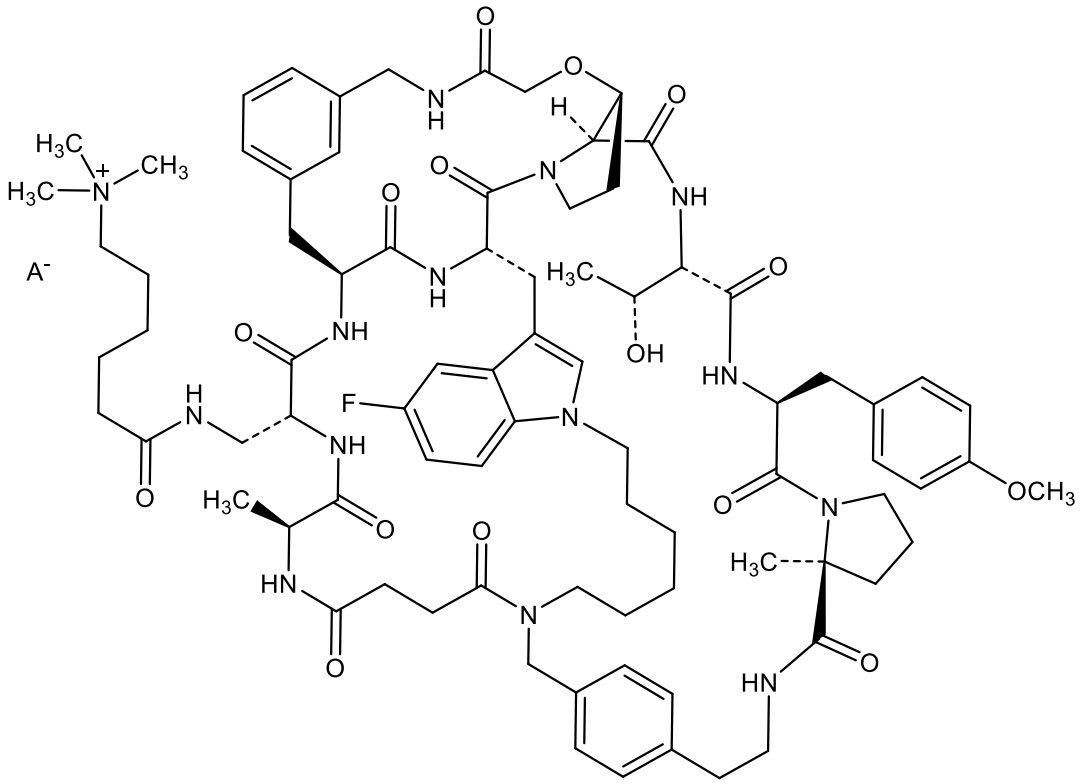
Fig. 1 depicts an X-ray powder diffraction pattern of Amorphous Acetate 1, showing a range of 2-40 2θ. The graph plots the intensity of the peaks as defined by counts per second versus the diffraction angle 2 theta (2θ) in degrees.

Fig. 2 depicts an X-ray powder diffraction pattern of Acetate 2, showing a range of 2-40 2θ. The graph plots the intensity of the peaks as defined by counts per second versus the diffraction angle 2 theta (2θ) in degrees.

Fig. 3 depicts an X-ray powder diffraction pattern of Acetate 3, showing a range of 2-40 2θ. The graph plots the intensity of the peaks as defined by counts per second versus the diffraction angle 2 theta (2θ) in degrees.

WHAT IS CLAIMED IS:

1. A crystalline form of a compound of Formula I:



I

wherein A^- is a pharmaceutically acceptable anion.

2. The crystalline form of claim 1, wherein the crystalline form is selected from Acetate 2, Acetate 3, Acetate 4, Acetate 5, Acetate 6, Caprate 2, Caprate 3, Caprate 4, Caprate 5, Caprate 6, Caprate 7, Caprate 8, Caprate 9, Caprate 10, Caprate 11, Caprate 12, Caprate 13, Caprate 14, D-Lactate 1, D-Lactate 2, Succinate 1, Succinate 2, L-Tartrate 1, L-Tartrate 2, Sulfate 1, and Sulfate 2.

3. The crystalline form of claims 1-2, wherein the crystalline form is Acetate 2, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles of (±0.2º) 4.92, 6.59, 9.82, and 17.91.

4. The crystalline form of claims 1-2, wherein the crystalline form is Acetate 3, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 4.48, 18.17, 18.79, and 19.27.

5. The crystalline form of claims 1-2, wherein the crystalline form is Acetate 4, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 8.36, 17.74, 20.29, and 21.35.

6. The crystalline form of claims 1-2, wherein the crystalline form is Acetate 5, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 5.02, 6.66, 9.89, and 19.84.

7. The crystalline form of claims 1-2, wherein the crystalline form is Acetate 6, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 7.79, 11.00, 16.24, and 18.89.

8. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 2, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 4.85, 7.65, 17.16, 18.20, and 19.50.

9. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 3, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 7.92, 15.40, 17.33, and 19.60.

10. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 4, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 4.18, 6.14, 17.51, and 17.68.

11. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 5, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 7.66, 16.18, 18.26, and 19.11.

12. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 6, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 5.33, 6.97, 19.04, and 21.58.

13. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 7, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 7.73, 17.14, 18.75, and 19.48.

14. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 8, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 7.45, 17.97, 19.32, and 22.08.

15. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 9, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 6.73, 11.95, 18.23, and 19.77.

16. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 10, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of about 3.50, 7.90, 16.21, and 18.23.

17. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 11, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of, 3.93, 4.90, and 7.68.

18. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 12, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 6.80, 15.37, 18.22, and 20.63.

19. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 13, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta at angles (±0.2º) of 5.02, 6.29, 7.12, and 20.25.

20. The crystalline form of claims 1-2, wherein the crystalline form is Caprate 14, wherein the crystalline form is characterized by an X-ray powder diffraction pattern having peaks expressed in degrees-2-theta radiation at angles (±0.2º) of 6.74, 18.16, 19.51, and 20.68.

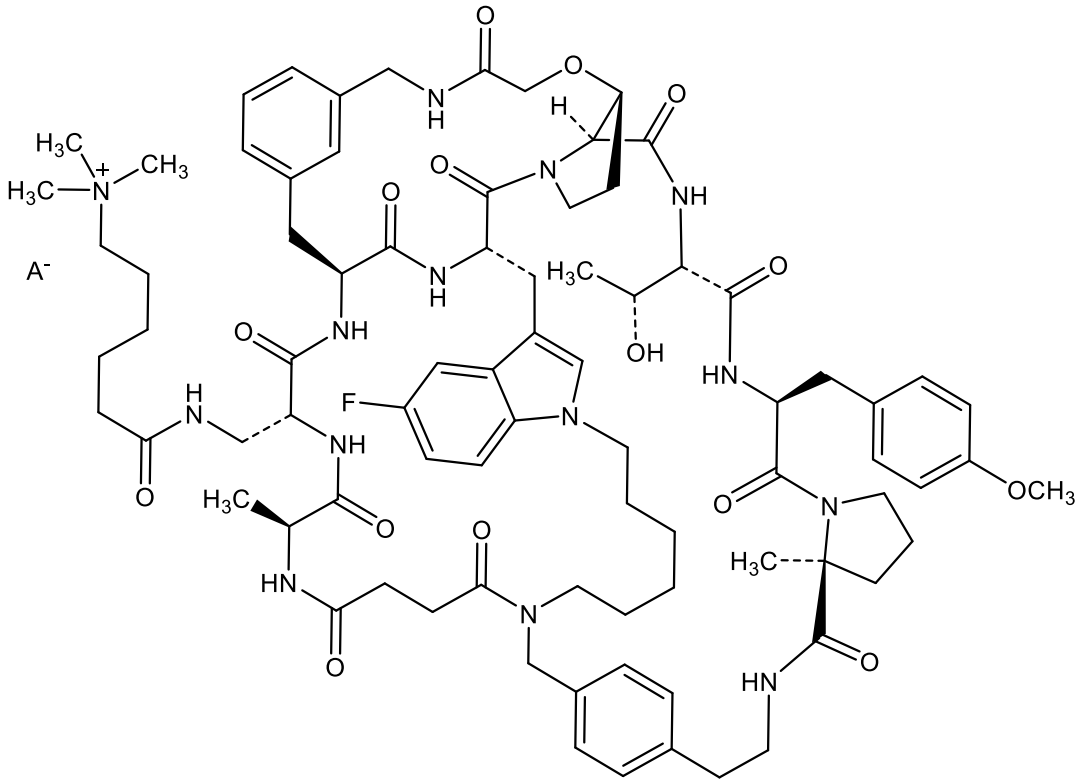
21. A pharmaceutical composition comprising at least one crystalline form according to any one of claims 1-20 and a pharmaceutically acceptable carrier.

22. Use of the crystalline form according to any one of claims 1-20 in the manufacture of a medicament for treating hypercholesterolemia.

23. Use of the crystalline form according to any one of claims 1-20 in the manufacture of a medicament for reducing LDL-C.

24. Use of the crystalline form according to any one of claims 1-20 in the manufacture of a medicament for treating atherosclerotic cardiovascular disease.

25. A crystalline form of a compound of Formula I:



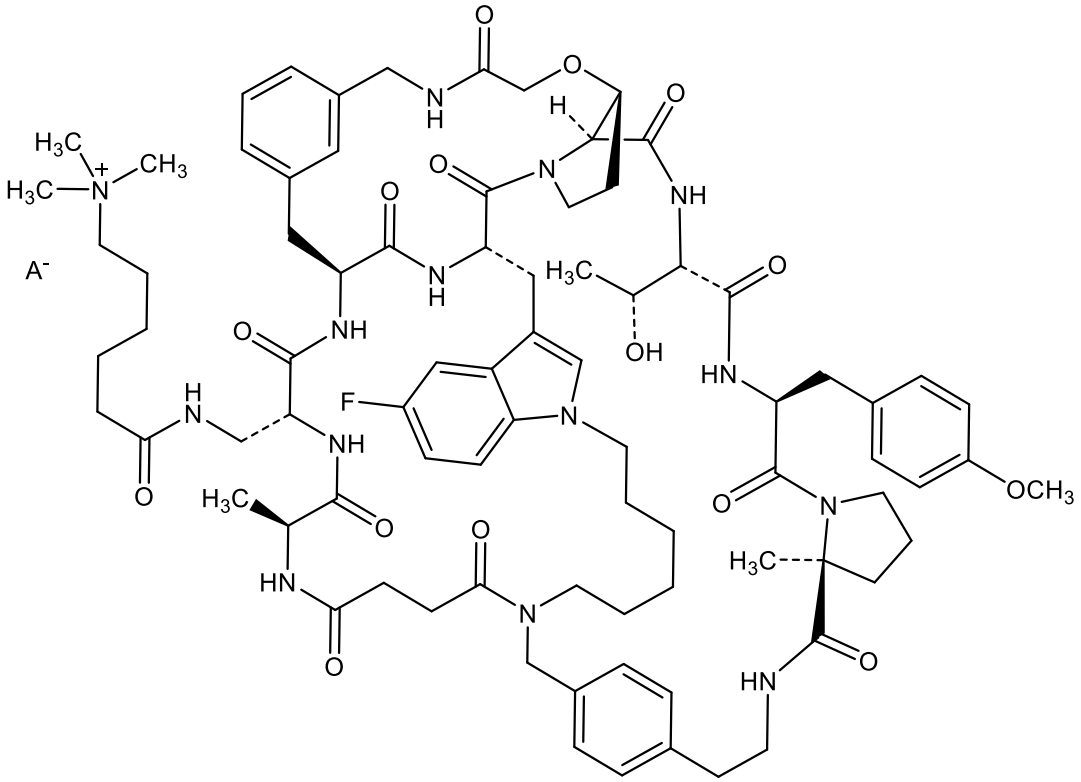
I

wherein A^- is a pharmaceutically acceptable anion;

formed by a process comprising adding an alcohol to a starting material,

wherein the starting material is selected from Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, and Compound 6.

26. The crystalline form, according to Claim 25, of a compound of Formula I:



I

wherein A^- is caprate;

formed by a process comprising adding an alcohol to a form of Compound 2.

27. The crystalline form of any one of claims 25-26, wherein the crystalline form is selected from Caprate 2, Caprate 3, Caprate 4, Caprate 5, Caprate 6, Caprate 7, Caprate 8, Caprate 9, Caprate 10, Caprate 11, Caprate 12, Caprate 13, and Caprate 14.

28. The crystalline form of any one of claims 25-27, wherein the alcohol is selected from: ethanol, propanol, or butanol.

29. The crystalline form of any one of claim 25-28, wherein the process comprises adding a solvent system to Compound 2, wherein the solvent system comprises MTBE, water, and the alcohol.

30. The crystalline form of claim 29, wherein the solvent system is comprised of MTBE, approximately 30-40% weight 1-propanol and 0.5-5% water.

31. The crystalline form of claim 30, wherein the crystalline form is Caprate 3 and the process further comprises filtering the solvent system resulting in the formation of a wet cake and drying the wet cake.

32. A crystalline form according to any one of claims 1-20 for use in inhibiting PCSK9 activity wherein the amount of the crystalline form of the compound of Formula I is from about 5 mg to about 300 mg.

33. A pharmaceutical composition, where the pharmaceutical composition comprises the crystalline form according to any one of claims 1-20, wherein the amount of the crystalline form of the compound of Formula I is from about 5 mg to about 300 mg, and the pharmaceutical composition comprises a permeation enhancer.

34. The pharmaceutical composition of claim 33, wherein the permeation enhancer is sodium caprate.

35. The pharmaceutical composition of claims 33-34, wherein the crystalline form of the compound of Formula I is Caprate 3.

36. Use of a pharmaceutical composition of any one of claims 21 or 33-35 in the manufacture of a medicament for the treatment of hypercholesterolemia.

37. Use of a pharmaceutical composition of any one of claims 21 or 33-35 in the manufacture of a medicament for the treatment of atherosclerotic cardiovascular disease.

38. Use of a pharmaceutical composition of any one of claims 21 or 33-35 in the manufacture of a medicament for reducing LDL-C.

39. A crystalline form according to any one of claims 1-20 for use in the treatment of hypercholesterolemia.

40. A crystalline form according to any one of claims 1-20 for use in the treatment of atherosclerotic cardiovascular disease.

41. A crystalline form according to any one of claims 1-20 for use in reducing LDL-C.