ClinicalTrials.gov includes disclosure of a research study to assess the safety, pharmacokinetics and pharmacodynamics of 25HC3S in patients with AH, with dose escalation including three doses: 30 mg, 90 mg, and 150 mg. See ClinicalTrials.gov Identifier: NCT03432260.

There is an urgent need for improved methods to treat AH.

SUMMARY

The present disclosure provides a variety of methods of treating alcoholic hepatitis (AH). The methods involve administering an effective amount of 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof. In certain instances, the methods involve administering an effective amount of 5-cholesten-3,25-diol, 3β-sulfate or salt thereof.

The results of the present disclosure are surprising for several reasons. For instance, in some ~~embodiments~~examples, the low dose of the present disclosure is surprising. Further, in some ~~embodiments~~examples, the low dose frequency is surprising. Still further, in some ~~embodiments~~examples, the low number of doses to attain efficacy in the treatment of AH is surprising. The results of the present disclosure are also surprising to the extent that the low dose amount, low dose frequency, and low total number of doses can provide results that are similar to or better than corticosteroids which require larger dose amounts, more frequent dosing, and/or a higher total number of doses. Still further, the present disclosure is also capable of achieving efficacious results in AH patients characterized by particular diagnostic criteria, such as Model for End-stage Liver Disease (MELD) score and/or other criteria discussed elsewhere herein.

In one aspect of the present disclosure, there is provided a use of 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof, in the manufacture of a medicament for treating alcoholic hepatitis in a human subject in need thereof, wherein the 25HC3S or salt thereof is to be administered to the human subject in an amount that is sufficient to treat the alcoholic hepatitis.

Further ~~aspects~~ embodiments of the disclosure:

1. A method of treating alcoholic hepatitis in a human subject in need thereof, the method comprising administering to the subject 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in an amount that is sufficient to treat the alcoholic hepatitis.

2. The method according to ~~aspect~~embodiment 1, wherein the administering comprises administering a total amount of the 25HC3S or salt thereof ranging from about 1 mg to about 1000 mg.

3. The method according to ~~aspect~~embodiment 1 or 2, wherein the administering comprises administering a total amount of the 25HC3S or salt thereof ranging either: (a) from about 10 mg/month to about 500 mg/month; or (b) from about 10 mg/month to about 400 mg/month.

4. The method according to any one of ~~aspect~~embodiments 1 to 3, the method comprising administering to the human subject a total amount of either: (a) about 10 mg/month to about 400 mg/month; or (b) about 10 mg to about 400 mg of 25HC3S or salt thereof in a period of one month; wherein:

- the total amount is sufficient to treat the alcoholic hepatitis;
- the total amount is administered in one or more separate doses comprising at least a first dose; and
- the period of one month is measured from the beginning of administration of the first dose.

5. The method of any one of ~~aspect~~embodiments 2 to 4, wherein the total amount is administered in from one to fifteen separate doses.

6. The method of any one of ~~aspect~~embodiments 2 to 4, wherein the total amount is administered in from one to five separate doses.

7. The method of any one of ~~aspect~~embodiments 2 to 4, wherein the total amount is administered in one dose or in two separate doses, preferably as a single dose.

8. The method of any one of ~~aspect~~embodiments 2 to 7, wherein the total amount is at least about 20 mg.

9. The method of any one of ~~aspect~~embodiments 2 to 8, wherein the total amount is not more than about 300 mg.

10. The method of any one of ~~aspect~~embodiments 2 to 8, wherein the total amount is not more than about 200 mg.

11. The method of any one of ~~aspect~~embodiments 2 to 8, wherein the total amount is not more than about 140 mg.

12. The method of any one of ~~aspect~~embodiments 4 to 11, wherein at least one, and preferably each, of the one or more separate doses comprises from about 10 mg to about 200 mg of 25HC3S or salt thereof.

13. The method of any one of ~~aspect~~embodiments 4 to 12, wherein at least one, and preferably each, of the one or more separate doses comprises from about 10 mg to about 120 mg of 25HC3S or salt thereof.

14. The method of any one of ~~aspect~~embodiments 4 to 13, wherein at least one, and preferably each, of the one or more separate doses comprises from about 20 mg to about 100 mg of 25HC3S or salt thereof.

15. The method of any one of ~~aspect~~embodiments 2 to 14, wherein the total amount is administered in two or more separate doses that are administered at a dose frequency ranging from daily to once every week.

16. The method of ~~aspect~~embodiment 15, wherein the dose frequency ranges from once every two days to once every week.

17. The method of ~~aspect~~embodiment 15, wherein the dose frequency ranges from once every two days to once every five days.

18. The method of ~~aspect~~embodiment 15, wherein the dose frequency ranges from once every two days to once every four days.

19. The method of ~~aspect~~embodiment 4, wherein:

- the total amount is administered in one dose or in two separate doses;
- the one dose comprises from about 10 mg to about 200 mg of 25HC3S or salt thereof;
- each of the two separate doses comprises from about 10 mg to about 200 mg of 25HC3S or salt thereof; and

- the two separate doses are administered at a dose frequency ranging from once every two days to once every four days.

20. The method of ~~aspect~~embodiment 19, wherein the total amount is administered in one dose and wherein the one dose comprises: (a) from about 20 mg to about 40 mg of 25HC3S or salt thereof; or (b) from about 80 mg to about 100 mg of 25HC3S or salt thereof; or (c) from about 140 mg to about 160 mg of 25HC3S or salt thereof.

21. The method of ~~aspect~~embodiment 19, wherein the total amount is administered in two separate doses and wherein each of the two separate doses comprises: (a) from about 20 mg to about 40 mg of 25HC3S or salt thereof; or (b) from about 80 mg to about 100 mg of 25HC3S or salt thereof; or (c) from about 140 mg to about 160 mg of 25HC3S or salt thereof.

22. The method of any one of ~~aspect~~embodiments 4 to 21, wherein a total amount per kg of 25HC3S or salt thereof that is administered in the period ranges from about 0.05 mg/kg to about 20 mg/kg.

23. The method of ~~aspect~~embodiment 22, wherein the total amount per kg ranges from about 0.1 mg/kg to about 10 mg/kg.

24. The method of ~~aspect~~embodiment 22, wherein the total amount per kg ranges from about 0.2 mg/kg to about 6 mg/kg.

25. The method of ~~aspect~~embodiment 22, wherein the total amount per kg ranges from about 0.3 mg/kg to about 1.5 mg/kg.

26. The method of any one of ~~aspect~~embodiments 1 to 25, wherein the administering is performed parenterally, intravenously, intramuscularly, or subcutaneously.

27. The method of any one of ~~aspect~~embodiments 1 to 26, wherein the administering is performed by injection.

28. The method of any one of ~~aspect~~embodiments 1 to 27, wherein the 25HC3S or salt thereof is administered in a formulation comprising the 25HC3S or salt thereof and a pharmaceutically acceptable carrier.

29. The method of any one of ~~aspect~~embodiments 1 to 28, wherein the 25HC3S or salt thereof comprises a salt of 25HC3S, wherein the salt of 25HC3S is preferably the sodium salt.

30. The method of any one of ~~aspect~~embodiments 4 to 29, wherein the one or more separate doses are administered over an administration period of not more than 14 days.

31. The method of any one of ~~aspect~~embodiments 1 to 30, wherein the human subject has a Model for End-stage Liver Disease (MELD) score of at least 11.

32. The method of any one of ~~aspect~~embodiments 1 to 31, wherein the human subject has a MELD score ranging from 11 to 45.

33. The method of any one of ~~aspect~~embodiments 1 to 32, wherein the human subject has a MELD score ranging from 15 to 40.

34. The method of any one of ~~aspect~~embodiments 1 to 33, wherein the human subject has a MELD score of at least 20.

35. The method of any one of ~~aspect~~embodiments 1 to 34, wherein the human subject has a MELD score of at least 30.

36. The method of any one of ~~aspect~~embodiments 1 to 35, wherein the human subject has a Maddrey's discriminant function (MDF) of at least 32.

37. The method of any one of ~~aspect~~embodiments 1 to 36, wherein the alcoholic hepatitis is characterized by reduced liver function that occurs within 13 weeks of onset.

38. The method of any one of ~~aspect~~embodiments 1 to 36, wherein the alcoholic hepatitis is characterized by reduced liver function that occurs within 10 weeks of onset.

39. The method of any one of ~~aspect~~embodiments 1 to 38, wherein the alcoholic hepatitis is characterized by reduced liver function such that the subject exhibits a reduced rate of clearance of 25HC3S as compared to a subject that does not have alcoholic hepatitis.

40. The method of ~~aspect~~embodiment 39, wherein the alcoholic hepatitis is characterized by reduced liver function such that the subject exhibits a rate of clearance of 25HC3S that is 50% or less, 40% or less, 30% or less, or 25% or less of the rate of clearance of 25HC3S from the plasma by a subject that does not have alcoholic hepatitis.

41. The method of any one of ~~aspect~~embodiments 1 to 40, wherein the alcoholic hepatitis is characterized by reduced liver function such that the subject exhibits a half-life time of 25HC3S in the plasma after administration ($T_{1/2}$) that is 1.5-fold greater or more, or 2-fold greater or more, as compared to a subject that does not have alcoholic hepatitis.

42. The method of any one of ~~aspect~~embodiments 1 to 41, wherein the subject exhibits a half-life time of 25HC3S in the plasma after administration ($T_{1/2}$) ranging from about 1.5 hours to about 6 hours or from about 2 hours to about 5 hours.

43. The method of any one of ~~aspect~~embodiments 1 to 42, wherein the subject exhibits a Cmax of 25HC3S ranging from about 500 ng/mL to about 10,000 ng/mL, from about 600 ng/mL to about 7000 ng/mL, or from about 700 ng/mL to about 5000 ng/mL.

44. The method of any one of ~~aspect~~embodiments 1 to 43, wherein the subject exhibits a Cmax of 25HC3S ranging from about 500 ng/mL to about 10,000 ng/mL, from about 600 ng/mL to about 7000 ng/mL, or from about 700 ng/mL to about 5000 ng/mL, per 100 mg of intravenously administered 25HC3S or salt thereof.

45. The method of any one of ~~aspect~~embodiments 1 to 44, wherein the subject exhibits an AUCinf of 25HC3S ranging from about 3000 ng*h/mL to about 50,000 ng*h/mL, about 4000 ng*h/mL to about 40,000 ng*h/mL, or from about 5000 ng*h/mL to about 30,000 ng*h/mL.

46. The method of any one of ~~aspect~~embodiments 1 to 45, wherein the subject exhibits an AUCinf of 25HC3S ranging from about 3000 ng*h/mL to about 50,000 ng*h/mL, about 4000 ng*h/mL to about 40,000 ng*h/mL, or from about 5000 ng*h/mL to about 30,000 ng*h/mL, per 100 mg of intravenously administered 25HC3S or salt thereof.

47. The method of any one of ~~aspect~~embodiments 1 to 46, wherein the subject exhibits a volume of distribution of 25HC3S ranging from about 10 L to about 50 L, about 15 L to about 45 L, or from about 20 L to about 40 L.

48. The method of any one of ~~aspect~~embodiments 1 to 47, wherein the subject exhibits a clearance of 25HC3S ranging from about 2 L to about 8 L/h, about 2.5 L/h to about 7.5 L/h, or from about 3 L/h to about 7 L/h.

49. The method of any one of ~~aspect~~embodiments 1 to 48, wherein the alcoholic hepatitis is characterized by loss of liver function that occurs within 13 weeks of onset.

50. The method of any one of ~~aspect~~embodiments 1 to 48, wherein the alcoholic hepatitis is characterized by loss of liver function that occurs within 10 weeks of onset.

51. 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof for use in a method of treating alcoholic hepatitis in a human subject in need thereof, wherein the method is as defined in any one of ~~aspect~~embodiments 1 to 50.

52. Use of 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in a method for the manufacture of a medicament for use in a method of treating alcoholic hepatitis in a human subject in need thereof, wherein the method is as defined in any one of ~~aspect~~embodiments 1 to 50.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. compares standard of care treatment (left) and treatment with 5-cholesten-3,25-diol, 3-sulfate (25HC3S) (right). The standard of care patients received supportive treatment with or without corticosteroids. The 25HC3S patients received one or two doses of 25HC3S sodium salt, with each dose at an amount of 30 mg, 90 mg, or 150 mg.

CLAIMS

1. Use of 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof, in the manufacture of a medicament for ~~A method of~~ treating alcoholic hepatitis in a human subject in need thereof, wherein the 25HC3S or salt thereof is to be administered ~~the method comprising administering~~ to the human subject ~~5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof~~ in an amount that is sufficient to treat the alcoholic hepatitis.

2. The ~~method~~ use according to claim 1, wherein ~~the administering comprises administering~~ a total amount of the 25HC3S or salt thereof ranging from about 1 mg to about 1000 mg is to be administered to the human subject.

3. The use ~~method~~ according to claim 1 or 2, wherein ~~the administering comprises administering~~ a total amount of the 25HC3S or salt thereof ranging from about 10 mg/month to about 400 mg/month is to be administered to the human subject.

4. The ~~method~~ use according to any one of claims 1 to 3, wherein ~~the method comprising administering to the human subject~~ a total amount of about 10 mg to about 400 mg of 25HC3S or salt thereof is to be administered to the human subject; in a period of one month, wherein:

- the total amount is sufficient to treat the alcoholic hepatitis;
- the total amount is to be administered in one or more separate doses comprising at least a first dose; and
- the period of one month is measured from the beginning of administration of the first dose.

5. The ~~method~~ use of any one of claims 2 to 4, wherein the total amount is to be administered in one dose or in two separate doses, preferably as a single dose.

6. The ~~method~~ use of any one of claims 4 to 5, wherein at least one, and preferably each, of the one or more separate doses comprises from about 10 mg to about 200 mg of 25HC3S or salt thereof.

7. The ~~method~~ use of any one of claims 4 to 6, wherein at least one, and preferably each, of the one or more separate doses comprises from about 20 mg to about 100 mg of 25HC3S or salt thereof.

8. The ~~method~~ use of any one of claims 2 to 7, wherein the total amount is to be administered in two or more separate doses that are administered at a dose frequency ranging from daily to once every week.

9. The ~~method~~ use of claim 4, wherein:

- the total amount is to be administered in one dose or in two separate doses;
- the one dose comprises from about 10 mg to about 200 mg of 25HC3S or salt thereof;
- each of the two separate doses comprises from about 10 mg to about 200 mg of 25HC3S or salt thereof; and
- the two separate doses are to be administered at a dose frequency ranging from once every two days to once every four days.

10. The ~~method~~ use of any one of claims 1 to 9, wherein the 25HC3S or salt thereof is to be ~~administering is performed~~ parenterally, intravenously, intramuscularly, or subcutaneously administered.

11. The ~~method~~ use of any one of claims 1 to 10, wherein the 25HC3S or salt thereof ~~administering is performed~~ is to be administered by injection.

12. The ~~method~~ use of any one of claims 1 to 11, wherein the 25HC3S or salt thereof is to be administered in a formulation comprising the 25HC3S or salt thereof and a pharmaceutically acceptable carrier.

13. The ~~method~~ use of any one of claims 1 to 12, wherein the 25HC3S or salt thereof comprises a salt of 25HC3S, wherein the salt of 25HC3S is preferably the sodium salt.

~~14. 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof for use in a method of treating alcoholic hepatitis in a human subject in need thereof, wherein the method is as defined in any one of claims 1 to 13.~~

~~15. Use of 5-cholesten-3,25-diol, 3-sulfate (25HC3S) or salt thereof in a method for the manufacture of a medicament for use in a method of treating alcoholic hepatitis in a human subject in need thereof, wherein the method is as defined in any one of claims 1 to 13.~~