SUMMARY

In one aspect, the present disclosure refers to use of a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an individual with Crohn's Disease.

In one aspect, the present disclosure refers to use of Compound 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an individual with Crohn's Disease, wherein:

an induction dose of the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for an induction phase, wherein the induction phase comprises at least 14 weeks; and

a maintenance dose of the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for a maintenance phase.

In one aspect, the present disclosure refers to a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, for use in treatment of Crohn's Disease in an individual.

In one aspect, the present disclosure refers to a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, for use in treatment of Crohn's Disease in an individual, wherein:

an induction dose of the compound is to be administered to the individual for an induction phase, wherein the induction phase comprises at least 14 weeks; and

a maintenance dose of the compound is to be administered to the individual for a maintenance phase.

In one aspect, the present disclosure refers to use of a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of moderately to severely active Crohn's Disease in an individual.

In one aspect, the present disclosure refers to use of a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treatment of moderately to severely active Crohn's Disease in an individual, wherein:

an induction dose of the compound is to be administered to the individual for an induction phase, wherein the induction phase comprises at least 14 weeks; and

a maintenance dose of the compound is to be administered to the individual for a maintenance phase.

In one aspect, the present disclosure refers to use of Compound 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an individual with Crohn's Disease, wherein:

an induction dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for an induction phase, wherein the induction phase comprises at least 14 weeks;

the individual is to be tested for a clinical response; and

if the individual demonstrates a clinical response, a maintenance dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for a maintenance phase.

Also ~~P~~provided is a method of treating an individual with moderately to severely active Crohn's Disease comprising: administering to the individual in need thereof a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof.

In some ~~embodiment~~examples, a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, is for use in a method of treatment of Crohn's Disease in an individual, wherein the method of use includes administering an induction dose of the compound to the individual for an induction phase, wherein the induction phase is at least 14 weeks long, and administering a maintenance dose of the compound to the individual for a maintenance phase. In some ~~embodiment~~examples, the induction dose comprises an amount equivalent to 3 mg of Compound 1. In some ~~embodiment~~examples, the maintenance dose comprises an amount equivalent to 2 mg of Compound 1. In some ~~embodiment~~examples, the maintenance phase is at least 38 weeks. In some ~~embodiment~~examples, the compound is administered at a frequency of once a day during both the induction phase and the maintenance phase. In some ~~embodiment~~examples, the individual has moderately to severely active Crohn's Disease.

A phase 2 study demonstrated improved efficacy for 2 mg of Compound 1 over placebo in subjects with UC. However, a Phase 2 study with another selective S1P receptor modulator (amiselimod) did not result in improved efficacy over placebo in subjects with CD (*D'Haens G et al. Amiselimod, a selective S1P receptor modulator in Crohn's disease patients: A proof-of-concept study. J Crohn Colitis. 2019;13(Suppl):S055-S056*). Further, while UC and CD have overlapping features, there are differences in pathophysiology, disease location, and extent of disease that may dictate different doses for the treatment of UC and CD. Described herein is the elucidation of safe and efficacious dosing of Compound 1 for the treatment of CD.

These and other aspects of the ~~invention~~ disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

CLAIMS

What is claimed is:

1. ~~A method of treating an individual with Crohn's Disease comprising: administering to the individual in need thereof~~Use of a pharmaceutical dosage form comprising a therapeutically effective amount of (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an individual with Crohn's Disease.

2. The use~~method~~ of claim 1, wherein the individual has demonstrated an inadequate response to, loss of response to, or intolerance of to at least one agent for the treatment of Crohn's Disease chosen from glucocorticosteroids, immunosuppressants, and biologics.

3. The use~~method~~ of claim 1 or 2, wherein the dosage form is to be administered under fasted conditions.

4. The use~~method~~ of claim 1 or 2, wherein the dosage form is to be administered under fed conditions.

5. The use~~method~~ of any one of the preceding claims, wherein the therapeutically effective amount is equivalent to about 0.5 to about 5.0 mg of Compound 1.

6. The use~~method~~ of claim 5, wherein the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1.

7. The use~~method~~ of claim 5, wherein the therapeutically effective amount is in an amount equivalent to 3 mg of Compound 1.

8. The use~~method~~ of any one of the preceding claims, wherein the dosage form is to be administered without titration.

9. The use~~method~~ of claim 5, wherein the individual is to be administered an amount equivalent to 2 mg of Compound 1 for a first time period and subsequently an amount equivalent to 3 mg of Compound 1 for a second time period.

10. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof is to be administered orally.

11. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is formulated as a capsule or tablet suitable for oral administration.

12. The use~~method~~ of any one of the preceding claims, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is selected from:

Compound 1;

a calcium salt of Compound 1; and

an L-arginine salt of Compound 1.

13. The use~~method~~ of claim 12, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an L-arginine salt of Compound 1.

14. The use~~method~~ of claim 13, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of an L-arginine salt of Compound 1.

15. The use~~method~~ of claim 12, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of Compound 1.

16. The use~~method~~ of any one of the preceding claims, wherein the therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered once daily to the individual.

17. The use~~method~~ of any one of the preceding claims, wherein the use~~method~~ is non-gender specific.

18. The use~~method~~ of any one of the preceding claims, wherein the individual was previously administered at least one agent selected from: a TNFα antagonist, an integrin antagonist, and an immunosuppressive agent.

19. The use~~method~~ of claim 18, wherein the individual had an inadequate response with, lost response to, or was intolerant to the at least one agent.

20. The use~~method~~ of any one of the preceding claims, wherein treating comprises inducing and/or maintaining clinical response; improving endoscopic appearance of the mucosa; and/or inducing and/or maintaining clinical remission.

21. The use~~method~~ of any one of the preceding claims, wherein said ~~administering~~ use results in no serious adverse events.

22. The use~~method~~ of any one of the preceding claims, wherein the Compound 1 is to be administered without substantially inducing an acute heart rate reduction or heart block in the individual.

23. The use~~method~~ of any one of the preceding claims, ~~further comprising monitoring for~~ wherein adverse events during the administration of Compound 1, or a pharmaceutically acceptable salt thereof, is to be monitored and optionally, ~~interrupting or terminating~~ wherein the administration of Compound 1, or a pharmaceutically acceptable salt thereof, is to be interrupted or terminated.

24. The use~~method~~ of any one of the preceding claims, wherein said individual has moderately to severely active Crohn's Disease.

25. The use~~method~~ of claim 24, wherein said individual has moderately active Crohn's Disease.

26. The use~~method~~ of claim 24, wherein said individual has severely active Crohn's Disease.

27. The use~~method~~ of any one of the preceding claims, wherein said individual has had inadequate response to conventional therapy.

28. The use~~method~~ of claim 27, wherein said conventional therapy is selected from at least one of corticosteroids, immunosuppressants, and biologics.

29. The use~~method~~ of claim 27, wherein said conventional therapy is selected from at least one of prednisone, budesonide, 6-mercaptopurine, azathioprine, methotrexate, infliximab, adalimumab, or certolizumab pegol.

30. The use~~method~~ of any one of the preceding claims, wherein said individual is not to be co-administered a TNFα inhibitor.

31. The use~~method~~ of any one of the preceding claims, wherein Compound 1 is the sole active ingredient to be administered to the individual for treatment of said Crohn's Disease.

32. Use of Compound 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating an individual with Crohn's Disease ~~comprising,~~ wherein:

~~administering~~ an induction dose of the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for an induction phase, wherein the induction phase comprises at least 14 weeks; and

~~administering~~ a maintenance dose of the Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for a maintenance phase.

33. The use~~method~~ of claim 32, wherein the induction dose comprises an amount equivalent to 3 mg of Compound 1.

34. The use~~method~~ of any one of claim 32 or claim 33, wherein the maintenance dose comprises an amount equivalent to 2 mg of Compound 1.

35. The use~~method~~ of any one of claims 32-34, wherein the maintenance phase comprises at least 38 weeks.

36. The use~~method~~ of any one of claims 32-35, wherein the Compound 1 or a pharmaceutically acceptable salt thereof is to be administered at a frequency of once a day during both the induction dose and the maintenance dose.

37. The use~~method~~ of any one of claims 32-36, wherein said individual has moderately to severely active Crohn's disease.

38. A compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, for use in ~~a method of~~ treatment of Crohn's Disease in an individual.

39. A compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, for use in ~~a method of~~ treatment of Crohn's Disease in an individual, wherein ~~the method comprises~~:

~~administering~~ an induction dose of the compound is to be administered to the individual for an induction phase, wherein the induction phase comprises at least 14 weeks; and

~~administering~~ a maintenance dose of the compound is to be administered to the individual for a maintenance phase.

40. The compound for use according to claim 39, wherein the induction dose comprises an amount equivalent to 3 mg of Compound 1.

41. The compound for use according to claim 39 or 40, wherein the maintenance dose comprises an amount equivalent to 2 mg of Compound 1

42. The compound for use according to any one of claims 39-41, wherein the maintenance phase comprises at least 38 weeks.

43. The compound for use according to any one of claims 39-42, wherein the compound is to be administered at a frequency of once a day during both the induction dose and the maintenance dose.

44. The compound for use according to any one of claims 39-43, wherein said individual has moderately to severely active Crohn's Disease.

45. Use of a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in a method of~~ treatment of moderately to severely active Crohn's Disease in an individual.

46. Use of a compound that is (R)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[b]indol-3-yl)acetic acid (Compound 1), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in a method of~~ treatment of moderately to severely active Crohn's Disease in an individual, wherein ~~the method comprises~~:

~~administering~~ an induction dose of the compound is to be administered to the individual for an induction phase, wherein the induction phase comprises at least 14 weeks; and

~~administering~~ a maintenance dose of the compound is to be administered to the individual for a maintenance phase.

47. The use~~Use~~ according to claim 46, wherein the induction dose comprises an amount equivalent to 3.0 mg of Compound 1.

48. The use~~Use~~ according to claim 46 or 47, wherein the maintenance dose comprises an amount equivalent to 2.0 mg of Compound 1.

49. The use~~Use~~ according to any one of claims 46-48, wherein the maintenance phase comprises at least 38 weeks.

50. The use~~Use~~ according to any one of claims 46-49, wherein the compound is to be administered at a frequency of once a day during both the induction dose and the maintenance dose.

51. Use of Compound 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for~~A method of~~ treating an individual with Crohn's Disease ~~comprising~~, wherein:

~~administering~~ an induction dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for an induction phase, wherein the induction phase comprises at least 14 weeks;

~~testing~~ the individual is to be tested for a clinical response; and

if the individual demonstrates a clinical response, ~~administering~~ a maintenance dose of Compound 1, or a pharmaceutically acceptable salt thereof, is to be administered to the individual in need thereof for a maintenance phase.

52. The use~~method~~ of claim 51, wherein the induction dose comprises an amount equivalent to 3 mg of Compound 1.

53. The use~~method~~ of any one of claim 51 or claim 52, wherein the maintenance dose comprises an amount equivalent to 2 mg of Compound 1.

54. The use~~method~~ of any one of claims 51-53, wherein the maintenance phase comprises at least 38 weeks.

55. The use~~method~~ of any one of claims 51-54, wherein the Compound 1 or a pharmaceutically acceptable salt thereof is to be administered at a frequency of once a day during both the induction dose and the maintenance dose.

56. The use~~method~~ of any one of claims 51-55, wherein said individual has moderately to severely active Crohn's disease.

57. The use~~method~~ of any one of claims 51-56, wherein the clinical response is a Simple Endoscopic Score in Crohn's Disease (SES-CD) less than or equal to 4 and at least 2-point reduction from baseline with no sub-score > 1.

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58. The use~~method~~ of any one of claims 51-56, wherein the clinical response is a greater than or equal to 50% decrease from baseline in SES-CD.