There remains a great unmet clinical need for new efficacious and safe treatments for EoE, as current therapies often provide only transient or marginal symptomatic relief. The present disclosure satisfies this need and provides related advantages as well.

Citation of any reference throughout this application is not to be construed as an admission that such reference is prior art to the present application.

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 or ameliorating at least one symptom or indication of an eosinophilic GI disease in an individual in need thereof. Also ~~P~~provided is a method of treating or ameliorating at least one symptom or indication of an eosinophilic GI disease in an individual in need thereof, 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 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 or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) in an individual in need thereof. Also ~~P~~provided is a method of treating or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) in an individual in need thereof 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.

Provided is a method of treating, preventing or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) comprising: selecting an individual who exhibits at least one symptom or indication of EoE, wherein the individual has an elevated level of a biomarker selected from esophagus eosinophils, eotaxin-3, periostin, serum IgE (total and allergen-specific), IL-13, IL-5, TARC, TSLP, serum ECP, and EDN; and administering to the individual in need thereof 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.

Also provided is a method of treating, preventing or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) comprising: selecting an individual having an allergic reaction to an allergen that renders the individual susceptible to EoE; and 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 one aspect, the present disclosure refers to use of 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 eosinophilic esophagitis (EoE) in an individual in need thereof. Also provided is a method of treating eosinophilic esophagitis (EoE) including administering to an individual in need thereof 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, the individual in need thereof exhibits ≥15 eosinophils per high powered field (hpf) in the individual's esophagus prior to or at the time of the treatment ("baseline"). In some ~~embodiment~~examples, the individual in need thereof exhibits at least 30% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof. According to some ~~embodiment~~examples, the Compound 1, or a pharmaceutically acceptable salt thereof is administered under fasted conditions. According to some ~~embodiment~~examples, the Compound 1, or a pharmaceutically acceptable salt thereof is administered under fed conditions. In some ~~embodiment~~examples, the therapeutically effective amount is equivalent to about 0.5 to about 5.0 mg of Compound 1. In some ~~embodiment~~examples, the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1. In some ~~embodiment~~examples, the therapeutically effective amount is in an amount equivalent to 1 mg of Compound 1. According to some ~~embodiment~~examples, the therapeutically effective amount is administered at a frequency of once per day. In some ~~embodiment~~examples, the therapeutically effective amount is administered in the morning. In some ~~embodiment~~examples, the individual exhibits an esophageal PEC of less than 15 eos/hpf from baseline following the administration of Compound 1, or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the individual exhibits an esophageal PEC of less than 6 eos/hpf from baseline following the administration of Compound 1, or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the individual exhibits at least 50% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, the individual exhibits at least 40% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof. In some ~~embodiment~~examples, individual exhibits at least 50% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof. According to some ~~embodiment~~examples, the administering results in no serious adverse events. In some ~~embodiment~~examples, the Compound 1, or a pharmaceutically acceptable salt

thereof, is administered without substantially inducing an acute heart rate reduction or heart block in the individual.

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

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: The pathogenesis of EoE is shown. In step 1, esophageal epithelial cells polarize dendritic cells to a Th2 phenotype. In step 2, dendritic cells migrate to a lymph node (LN) and promote Th2 T cell differentiation. In step 3, newly activated Th2 cells leave the LN. In step 4, Th2 cells migrate to the esophagus and secrete cytokines. In step 5, eosinophils are recruited to the esophagus via the Th2 cytokines.

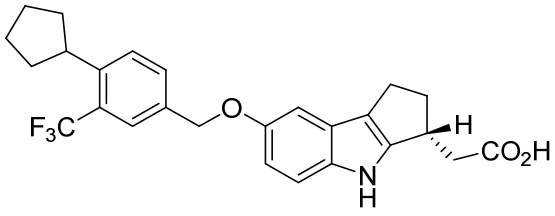
Figure 2: Endoscopic manifestations in adult EoE patients enrolled in a European multicenter trial are shown: white exudate (**a**), longitudinal furrows (**b**), diffuse edema (**c**), fixed rings (**d**), severe stricture (**e**), and rings, furrows and edema (**f**).

Figure 3 shows the effect of Compound 1 on the mean percent change from baseline to day 7 in immune cell subtypes, as further described in Example 3.

DETAILED DESCRIPTION

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

COMPOUND 1: As used herein, "Compound 1" means (*R*)-2-(7-(4-cyclopentyl-3-(trifluoromethyl)benzyloxy)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl)acetic acid including crystalline forms thereof.



(Compound 1)

See PCT patent application, Serial No. PCT/US2009/004265 hereby incorporated by reference in its entirety. As a non-limiting example, Compound 1 may be present as an anhydrous, non-solvated crystalline form as described in WO 2010/011316 (incorporated by reference herein in its

CLAIMS

What is claimed is:

1. ~~A method of treating or ameliorating at least one symptom or indication of an eosinophilic GI disease in an individual in need thereof, 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 or ameliorating at least one symptom or indication of an eosinophilic GI disease in an individual in need thereof.

2. The use~~method~~ of claim 1, wherein the eosinophilic GI disease is selected from eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC).

3. ~~A method of treating or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) in an individual in need thereof, 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 or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) in an individual in need thereof.

~~4. A method of treating, preventing or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) comprising:~~

~~selecting an individual who exhibits at least one symptom or indication of EoE, wherein the individual has an elevated level of a biomarker selected from esophagus eosinophils, eotaxin-3, periostin, serum IgE (total and allergen-specific), IL-13, IL-5, TARC, TSLP, serum ECP, and EDN; and~~

~~administering to the individual in need thereof 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.~~

~~5.~~4. The use~~method~~ of any one of the preceding claims~~claim 4~~, ~~wherein~~ comprising selecting the individual ~~is selected~~ on the basis of exhibiting ≥15 eosinophils per high powered field (hpf) in the esophagus prior to or at the time of the treatment ("baseline").

~~6.~~5. The use~~method~~ of any one of the preceding claims, wherein the individual exhibits at least 50% decrease in the number of eosinophils per hpf from baseline at day 10 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.

~~7. The method of claim 4, wherein the individual is selected on the basis of exhibiting an eotaxin-3 level of greater than about 50 pg/mL prior to or at the time of initiation of treatment ("baseline").~~

~~8. The method of claim 7, wherein the individual exhibits at least 50% decrease in eotaxin-3 level from baseline at day 10 following the administration.~~

~~9. The method of any one of claims 1 to 8, wherein the individual exhibits an allergic reaction to a food allergen contained in a food item selected from a dairy product, egg, wheat, soy, corn, fish, shellfish, peanut, a tree nut, beef, chicken, oat, barley, pork, green beans, apple and pineapple.~~

~~10. The method of any one of claims 1 to 9, wherein the individual exhibits an allergic reaction to a non-food allergen derived from one of dust, pollen, mold, plant, cat, dog or insect.~~

~~11. A method of treating, preventing or ameliorating at least one symptom or indication of eosinophilic esophagitis (EoE) comprising:~~

~~selecting an individual having an allergic reaction to an allergen that renders the individual susceptible to EoE; and~~

~~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.~~

~~12. The method of claim 11, wherein the allergen is a food allergen contained in a food item selected from a dairy product, egg, wheat, soy, corn, fish, shellfish, peanut, a tree nut, beef, chicken, oat, barley, pork, green beans, apple and pineapple.~~

~~13. The method of claim 11 or 12, wherein the allergen is a non-food allergen derived from one of dust, pollen, mold, plant, cat, dog or insect.~~

~~14. The method of any one of the preceding claims, wherein the symptom or indication of EoE is selected from eosinophilic infiltration of the esophagus, thickening of the esophageal wall, food refusal, vomiting, abdominal pain, heartburn, regurgitation, dysphagia and food impaction.~~

~~15.~~6. The use~~method~~ of any one of the preceding claims, wherein the administration of Compound 1, or a pharmaceutically acceptable salt thereof, results in reducing the level of an EoE-associated biomarker in the individual.

~~16.~~7. The use~~method~~ of claim ~~15~~6, wherein the EoE-associated biomarker is selected from esophagus eosinophils, eotaxin-3, periostin, serum IgE (total and allergen-specific), IL-13, IL-5, serum thymus and activation regulated chemokine (TARC), thymic stromal lymphopoietin (TSLP), serum eosinophilic cationic protein (ECP), and eosinophil-derived neurotoxin (EDN).

~~17. The method of any one of the preceding claims, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is administered in combination with a second therapeutic agent or therapy, wherein the second therapeutic agent or therapy is selected from an IL-1beta inhibitor, an IL-5 inhibitor, an IL-9 inhibitor, an IL-13 inhibitor, an IL-17 inhibitor, an IL-25 inhibitor, a TNFα inhibitor, an eotaxin-3 inhibitor, an IgE inhibitor, a prostaglandin D2 inhibitor, an immunosuppressant, a glucocorticoid, a proton pump inhibitor, a NSAID, allergen removal and diet management.~~

~~18. The method of any one of the preceding claims, wherein the individual, prior to or at the time of administration of Compound 1, or a pharmaceutically acceptable salt thereof, has or is diagnosed with a disease or disorder selected from atopic dermatitis, asthma, allergic rhinitis and allergic conjunctivitis.~~

~~19. The method of any one of the preceding claims, wherein the individual has demonstrated an inadequate response to, loss of response to, or intolerance of to at least one therapeutic agent or therapy.~~

~~20. The method of any one of the preceding claims, wherein the dosage form is administered under fasted conditions.~~

~~21. The method of any one of claims 1 to 19, wherein the dosage form is administered under fed conditions.~~

~~22.~~8. 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.

~~23. The method of claim 22, wherein the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1.~~

~~24.~~9. The use~~method~~ of claim ~~22~~8, 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.

~~25.~~10. The use~~method~~ of claim ~~22~~8, wherein the therapeutically effective amount is in an amount equivalent to 3 mg of Compound 1.

~~26. The method of any one of the preceding claims, wherein the dosage form is administered without titration.~~

~~27.~~11. 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.

~~28. The 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.~~

~~29. The 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.~~

~~30. The method of claim 29, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an L-arginine salt of Compound 1.~~

~~31. The method of claim 30, 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.~~

~~32. The method of claim 29, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is an anhydrous, non-solvated crystalline form of Compound 1.~~

~~33.~~12. 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.

~~34. The method of any one of the preceding claims, wherein the method is non-gender specific.~~

~~35. The method of any one of the preceding claims, wherein the individual was previously administered at least one therapeutic agent or therapy.~~

~~36. The method of claim 35, wherein the individual had an inadequate response with, lost response to, or was intolerant to the at least one therapeutic agent or therapy.~~

~~37. The method of any one of the preceding claims, wherein treating comprises inducing and/or maintaining clinical response and/or inducing and/or maintaining clinical remission.~~

~~38. The method of any one of the preceding claims, wherein treating comprises inducing and/or maintaining a histologic response via eosinophils per high power field ≤6.~~

~~39. The method of any one of the preceding claims, wherein said administering results in no serious adverse events.~~

~~40. The method of any one of the preceding claims, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is administered without substantially inducing an acute heart rate reduction or heart block in the individual.~~

~~41. The method of any one of the preceding claims, further comprising monitoring for adverse events during the administration of Compound 1, or a pharmaceutically acceptable salt thereof, and optionally, interrupting or terminating the administration of Compound 1, or a pharmaceutically acceptable salt thereof.~~

~~42.~~13. ~~A method of treating eosinophilic esophagitis (EoE) comprising:~~

~~administering to an individual in need thereof~~Use of 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 eosinophilic esophagitis (EoE) in an individual in need thereof.

~~43.~~14. The use~~method~~ of claim ~~42~~13, wherein the individual in need thereof exhibits ≥15 eosinophils per high powered field (hpf) in the individual's esophagus prior to or at the time of the treatment ("baseline").

~~44.~~15. The use~~method~~ of claim ~~42~~ 13 or ~~43~~14, wherein the individual in need thereof exhibits at least 30% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.

~~45. The method of any one of claims 42-44, wherein the dosage form is administered under fasted conditions.~~

~~46. The method of any one of claims 42-44, wherein the dosage form is administered under fed conditions.~~

~~47.~~16. The use~~method~~ of any one of claims ~~42-46~~13 to 15, wherein the therapeutically effective amount is equivalent to about 0.5 to about 5.0 mg of Compound 1.

~~48. The method of claim 47, wherein the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1.~~

~~49. The method of claim 47, wherein the therapeutically effective amount is in an amount equivalent to 1 mg of Compound 1.~~

~~50.~~17. The use~~method~~ of any one of claims ~~42-49~~13 to 16, wherein the therapeutically effective amount is to be administered at a frequency of once per day.

~~51. The method of any one of claims 42-50, wherein the therapeutically effective amount is administered in the morning.~~

~~52.~~18. The use~~method~~ of any one of claims ~~42-51~~13 to 17, wherein the individual exhibits an esophageal PEC of less than 15 eos/hpf from baseline following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.

~~53.~~19. The use~~method~~ of any one of claims ~~42-52~~13 to 18, wherein the individual exhibits an esophageal PEC of less than 6 eos/hpf from baseline following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.

~~54.~~20. The use~~method~~ of any one of claims ~~42-53~~13 to 19, wherein the individual exhibits at least 30% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.

~~55. The method of any one of claims 42-54, wherein the individual exhibits at least 40% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.~~

~~56. The method of any one of claims 42-55, wherein the individual exhibits at least 50% decrease in the number of eosinophils per hpf from baseline at week 16 following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.~~

~~57. The method of any one of claims 42-56, wherein said administering results in no serious adverse events.~~

~~58. The method of any one of claims 42-57, wherein Compound 1, or a pharmaceutically acceptable salt thereof, is administered without substantially inducing an acute heart rate reduction or heart block in the individual.~~

~~59. 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 eosinophilic esophagitis (EoE) in an individual, wherein the method comprises:~~

~~administering to an individual in need thereof 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.~~

~~60. The compound for use according to claim 59, the therapeutically effective amount is equivalent to about 0.5 to about 5.0 mg of Compound 1.~~

~~61. The compound for use according to claim 60, the therapeutically effective amount is equivalent to 1 mg of Compound 1.~~

~~62. The compound for use according to claim 60, the therapeutically effective amount is equivalent to 2 mg of Compound 1.~~

~~63. The compound for use according to claim 60, the therapeutically effective amount is equivalent to 3 mg of Compound 1.~~

~~64. The compound for use according to any one of claims 59-63, wherein the therapeutically effective amount is administered at a frequency of once per day.~~

~~65. The compound for use according to any one of claims 59-64, wherein the individual in need thereof exhibits ≥15 eosinophils per high powered field (hpf) in the individual's esophagus prior to or at the time of the treatment ("baseline").~~

~~66. The compound for use according to any one of claims 59-65, wherein the individual exhibits an esophageal PEC of less than 15 eos/hpf from baseline following the administration of Compound 1, or a pharmaceutically acceptable salt thereof.~~

~~67. The compound for use according to any one of claims 59-66, wherein said administering results in no serious adverse events.~~

~~68. The compound for use according to any one of claims 59-67, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, is administered without substantially inducing an acute heart rate reduction or heart block in the individual.~~