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 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 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 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 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 examples, the Compound 1, or a pharmaceutically acceptable salt thereof is administered under fasted conditions. According to some examples, the Compound 1, or a pharmaceutically acceptable salt thereof is administered under fed conditions. In some examples, the therapeutically effective amount is equivalent to about 0.5 to about 5.0 mg of Compound 1. In some examples, the therapeutically effective amount is in an amount equivalent to 2 mg of Compound 1. In some examples, the therapeutically effective amount is in an amount equivalent to 1 mg of Compound 1. According to some examples, the therapeutically effective amount is administered at a frequency of once per day. In some examples, the therapeutically effective amount is administered in the morning. In some 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 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 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 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 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 examples, the administering results in no serious adverse events. In some 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 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.

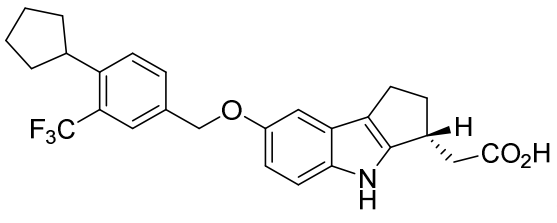
Figure 2: Endoscopic manifestations in adult EoE patients enrolled in a European multicenter trial are shown: white exudate (**a**), longitudinal furrows (**b**), diffuse edema (**c**), fixed rings (**d**), severe stricture (**e**), and rings, furrows and edema (**f**).

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. 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 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. 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. The use of any one of the preceding claims, comprising selecting the individual 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").

5. The use 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.

6. The use 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.

7. The use of claim 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).

8. The use 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.

9. The use of claim 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.

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

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

12. The use 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.

13. 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.

14. The use of claim 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").

15. The use of claim 13 or 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.

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

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

18. The use of any one of claims 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.

19. The use of any one of claims 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.

20. The use of any one of claims 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.