antibodies were shown to surprisingly and significantly reduce esophageal eosinophil count in esophageal biopsies of patients with EoE.

In one example, the instant disclosure provides for a method of treating eosinophilic esophagitis (EoE) in a subject, comprising subcutaneously administering about 180 mg to about 360 mg of an IL-13 antibody, or antigen binding fragment thereof, to the subject weekly, thereby treating EoE in the subject.

In one aspect, the present disclosure refers to use of a 13C5.5 antibody, or antigen binding fragment thereof, in the manufacture of a medicament for the treatment of eosinophilic esophagitis (EoE) in a subject.

In one example, the IL-13 antibody, or antigen-binding fragment thereof binds to IL-13 and prevents interaction between IL-13 and an IL-13 receptor. In one example, the IL-13 antibody, or antigen-binding portion thereof, is a monoclonal antibody, or antigen-binding portion thereof. In one example, the IL-13 antibody, or antigen-binding portion thereof, is a humanized antibody, or antigen-binding portion thereof. In one example, the IL-13 antibody, or antigen-binding portion thereof, is a human antibody, or antigen-binding portion thereof.

In one example, the IL-13 antibody, or antigen-binding fragment thereof, is the antibody 13C5.5, or an antigen binding fragment thereof. In one example, the 13C5.5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region comprising SEQ ID NO: 2 and a light chain variable region comprising SEQ ID NO: 3.

In another example, the anti-IL-13 antibody is 6A1, 3G4, tralokinumab, lebrikizumab, QAZ-576, IMA-638 or IMA-026, or an antigen-binding portion thereof.

In one example, the method comprises subcutaneously administering about 180 mg of the IL-13 antibody, or antigen binding fragment thereof, to the subject weekly. In another example, the method comprises subcutaneously administering about 360 mg of the IL-13 antibody, or antigen binding fragment thereof, to the subject weekly.

In one example, the method further comprises a step of selecting a subject who exhibits at least one symptom associated with EoE. In one example, the symptom associated with EoE is selected from the group consisting of eosinophilic infiltration of the esophagus, thickening of the esophageal wall, food refusal, vomiting, abdominal pain, heartburn, regurgitation, dysphagia, and food impaction.

In one example, the method further comprises selecting a subject who also has a disease or disorder selected from the group consisting of atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, and a combination thereof.

In one example, the selection step comprises selecting a subject based on an elevated level of a biomarker associated with eosinophilic esophagitis (EoE). In one example, the biomarker selected from the group consisting of esophagus eosinophils,

eotaxin-3, periostin, serum IgE, IL-13, IL-5, serum thymus and activation regulated chemokine (TARC; CCL17), thymic stromal lymphopoietin (TSLP), serum ECP, and eosinophil-derived neurotoxin (EDN) or a combination thereof.

In one example, the selection step comprises selecting a subject based on the mean esophageal eosinophil count in a biopsy sample obtained from the subject during an esophageal endoscopy. In one example, the selection step comprises selecting a subject based on peak eosinophil count of ≥15 per high powered field (HPF) in the esophagus.

In one example, the subject exhibits at least 50% decrease in the number of eosinophils per HPF from the peak level after at least 16 weeks of administration of the IL-13 antibody, or antigen binding fragment thereof.

In one example, the subject is a steroid naïve subject who has not previously undergone steroid therapy. In another example, the subject is a human subject who has previously undergone steroid therapy. In one example, the subject is a human subject who has previously undergone steroid therapy and is non-steroid refractory. In another example, the subject is a human subject who has previously undergone steroid therapy and is steroid refractory.

In one example, the antibody, or antigen-binding portion thereof, is administered to the subject for at least about 16 weeks. In another example, the antibody, or antigen-binding portion thereof, is administered to the subject for the duration of EoE disease.

In one example, the method comprises determining a mean esophageal eosinophil count measured in the 5 most inflamed high powered field (HPF) in the esophagus before administration of the antibody, or antigen-binding portion thereof, to the subject. In another example, the method comprises determining the mean esophageal eosinophil count measured in the 5 most inflamed high powered field (HPF) in the esophagus after administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, a decrease in the mean esophageal eosinophil count after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the mean esophageal eosinophil count before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method comprises determining dysphagia clinical symptoms before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the dysphagia clinical symptoms after administration of the antibody, or antigen-

binding portion thereof, to the subject, wherein a decrease in the dysphagia clinical symptoms after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the dysphagia clinical symptoms before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method comprises determining eosinophilic esophagitis activity index (EEsAI) and recorded as a daily symptom diary (DSD) before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the eosinophilic esophagitis activity index (EEsAI) and recorded as a daily symptom diary (DSD) after administration of the antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the EEsAI after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the EEsAI before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method comprises determining dysphagia symptom questionnaire (DSQ) score before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the DSQ score after administration of the antibody, or antigen-binding portion thereof, to the subject; wherein a decrease in the DSQ score after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the DSQ score before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method comprises determining endoscopic reference score (EREF) before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the EREF score after administration of the antibody, or antigen-binding portion thereof, to the subject; wherein a decrease in the EREF score after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the EREF score before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the EREF is determined based on the presence of inflammatory markers in the esophagus, the presence of remodeling markers in the esophagus, or a combination thereof. In one example, the EREF is determined based on the presence or absence of plurality of features selected from the group consisting of edema, fixed rings, exudates, furrows and stricture, or a combination thereof.

In one example, the method comprises determining a subject's global assessment of disease severity before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the subject's global

assessment of disease severity after administration of the antibody, or antigen-binding portion thereof, to the subject; wherein a decrease in the a subject's global assessment of disease severity after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the a subject's global assessment of disease severity before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method comprises determining a clinician's global assessment of disease severity before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the clinician's global assessment of disease severity after administration of the antibody, or antigen-binding portion thereof, to the subject; wherein a decrease in the a clinician's global assessment of disease severity after administration of the antibody, or antigen-binding portion thereof, to the subject as compared to the clinician's global assessment of disease severity before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method comprises determining a histology grade and a mean stage-adjusted score (HGMSAS) before administration of the antibody, or antigen-binding portion thereof, to the subject. In one example, the method comprises determining the HGMSAS after administration of the antibody, or antigen-binding portion thereof, to the subject; wherein a decrease in the HGMSAS after administration of the antibody, or antigen-binding portion thereof, to the HGMSAS before administration indicates that the antibody, or antigen-binding portion thereof, is effective in treating the subject.

In one example, the method further comprises administration of an additional agent. In one example, the additional agent is a steroid. In one example,, the additional agent is the steroid compound budesonide. In one example,, the additional agent is selected from the group consisting of: a therapeutic agent, an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof; methotrexate, a cyclosporin, a rapamycin, an FK506, a detectable label or reporter, a TNF antagonist, an anti-rheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an

antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an oral steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

In one example, the present disclosure provides compositions and methods for treating asthma. In one example, the instant disclosure provides for a method of treating asthma in a subject, comprising subcutaneously administering about 180 mg to about 360 mg of an IL-13 antibody, or antigen binding fragment thereof, to the subject weekly, thereby treating asthma in the subject.

In one example, the IL-13 antibody, or antigen-binding fragment thereof binds to IL-13 and prevents interaction between IL-13 and an IL-13 receptor. In one example, the antibody, or antigen-binding portion thereof, is a monoclonal antibody. In one example, the antibody, or antigen-binding portion thereof, is a humanized antibody. In one example, the antibody, or antigen-binding portion thereof, is a human antibody.

In one example, the antibody, or antigen-binding portion thereof, is a 13C5.5 antibody. In one example, the 13C5.5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region comprising SEQ ID NO: 2 and a light chain variable region comprising SEQ ID NO: 3.

In another example, the anti-IL-13 antibody is 6A1, 3G4, tralokinumab, lebrikizumab, QAZ-576, IMA-638 or IMA-026, or an antigen-binding portion thereof.

In one example, the method comprises subcutaneously administering about 180 mg of the IL-13 antibody, or antigen binding fragment thereof, to the subject weekly. In one example, the method comprises subcutaneously administering about 360 mg of the IL-13 antibody, or antigen binding fragment thereof, to the subject weekly.

In one example, the asthma is mild to moderate asthma.

In another example, the method further comprises selecting a subject who exhibits at least one symptom associated with asthma. In a related example, the at least one symptom associated with asthma selected from the group consisting of secretion or build-up of sticky mucus or phlegm, coughing, wheezing, shortness of breath, chest tightness, chest pain and chest pressure.

In one example, the subject is a human subject. In another example, the subject is a steroid naïve subject who has not previously undergone steroid therapy. In one example, the subject has previously undergone steroid therapy. In one example, the subject is a subject who has previously undergone steroid therapy, and the subject is non-steroid refractory. In another example, the subject is a subject who has previously undergone steroid therapy, and the subject is steroid refractory.

In one example, the antibody, or antigen binding fragment thereof, is administered to the subject weekly for at least about 16 weeks. In another example, the antibody, or antigen binding portion thereof, is administered to the subject weekly for the duration of EoE disease.

In one example, the method further comprises determining a biomarker associated with asthma before and after administration of the IL-13 antibody, or antigen binding fragment thereof, to the subject, wherein a change in the biomarker level indicates the efficacy of the IL-13 antibody, or antigen binding fragment thereof, in treating the subject.

In one example, the method further comprises administration of an additional agen. In one example, the additional agent is a steroid. In another example, the additional agent is budesonide. In yet another example, the additional agent is selected from the group consisting of: a therapeutic agent, an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof; methotrexate, a cyclosporin, a rapamycin, an FK506, a detectable label or reporter, a TNF antagonist, an anti-rheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an oral steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.

Other features and advantages of the disclosure will be apparent from the following description of the preferred examples thereof, and from the claims. References cited are hereby incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

Various features and advantages of the embodiments herein described can be fully appreciated as the same becomes better understood when considered in light of the accompanying drawings:

FIG. 1 shows mean esophageal eosinophil counts (cells/hpf) at baseline and at week 16 in the placebo group, low dose (180 mg) treatment group and high dose (360 mg) treatment group. Statistical significance was calculated by measuring p-values from

CLAIMS

We claim:

1. Use of a 13C5.5 antibody, or antigen binding fragment thereof, in the manufacture of a medicament for the treatment of eosinophilic esophagitis (EoE) in a subject.

2. The use according to claim 1, wherein said medicament is formulated for subcutaneous administration of a dosage amount of 180 mg to 360 mg, and wherein said administration is weekly.

3. The use of claim 2, wherein the 13C5.5 antibody, or antigen-binding fragment thereof, binds to IL-13 and prevents interaction between IL-13 and an IL-13 receptor.

4. The use of claim 2 or claim 3, wherein the 13C5.5 antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region comprising SEQ ID NO: 2 and a light chain variable region comprising SEQ ID NO: 3.

5. The use of any one of claims 2-4, wherein about 180 mg of the 13C5.5 antibody, or antigen binding fragment thereof, is to be administered subcutaneously to the subject weekly.

6. The use of any one of claims 2-4, wherein about 360 mg of the 13C5.5 antibody, or antigen binding fragment thereof, is to be administered subcutaneously to the subject weekly.

7. The use of any one of claims 2-6, wherein a subject who exhibits at least one symptom associated with eosinophilic esophagitis (EoE) is selected.

8. The use of claim 7, wherein the symptom associated with EoE is selected from the group consisting of eosinophilic infiltration of the esophagus, thickening of the esophageal wall, food refusal, vomiting, abdominal pain, heartburn, regurgitation, dysphagia, and food impaction.

9. The use of claim 7 or 8, wherein the subject also has a disease or disorder selected from the group consisting of atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, and a combination thereof.

10. The use of any one of claims 7-9, wherein the subject is selected based on an elevated level of a biomarker associated with eosinophilic esophagitis (EoE), wherein the biomarker is selected from the group consisting of esophagus eosinophils, eotaxin-3, periostin, serum IgE, IL-13, IL-5, serum thymus and activation regulated chemokine (TARC; CCL17), thymic stromal lymphopoietin (TSLP), serum ECP, eosinophil-derived neurotoxin (EDN), and a combination thereof.

11. The use of any one of claims 7-10, wherein the subject is selected based on the mean esophageal eosinophil counts in a biopsy sample obtained from the subject during an esophageal endoscopy.

12. The use of any one of claims 7-11, wherein the subject is selected based on peak eosinophil count of ≥15 per high powered field (HPF) in the esophagus.

13. The use of any one of claims 2-12, wherein the subject exhibits at least 50% decrease in the number of eosinophils per HPF from the peak level after at least 16 weeks of administration of the 13C5.5 antibody, or antigen binding fragment thereof.

14. The use of any one of claims 2-13, wherein the subject is a human subject.

15. The use of any one of claims 2-14, wherein the subject is a steroid naïve subject who has not previously undergone steroid therapy.

16. The use of any one of claims 2-14, wherein the subject has previously undergone steroid therapy.

17. The use of claim 16, wherein the subject is non-steroid refractory.

18. The use of claim 16, wherein the subject is steroid-refractory.

19. The use of any one of claims 2-18, wherein the 13C5.5 antibody, or antigen-binding portion thereof, is to be administered to the subject for at least about 16 weeks.

20. The use of any one of claims 2-19, wherein the 13C5.5 antibody, or antigen-binding portion thereof, is to be administered to the subject for the duration of EoE disease.

21. The use of any one of claims 2-20, wherein:
(i) a mean esophageal eosinophil count is to be determined by measuring the mean esophageal eosinophil count in the 5 most inflamed high powered field (HPF) in the esophagus before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the mean esophageal eosinophil count after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the mean esophageal eosinophil count before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject;
(ii) dysphagia clinical symptoms are to be determined before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the dysphagia clinical symptoms after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the dysphagia clinical symptoms before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject;
(iii) a dysphagia symptom questionnaire (DSQ) score is to be determined before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the DSQ score after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the DSQ score before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject;
(iv) mean eosinophilic esophagitis (EoE) endoscopic reference score (EREF) is to be determined before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the EREF after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the EREF before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject;

(v) a subject's global assessment of disease severity is to be determined before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the subject's global assessment of disease severity after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the subject's global assessment of disease severity before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject;
(vi) a clinician's global assessment of disease severity is to be determined before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the clinician's global assessment of disease severity after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the clinician's global assessment of disease severity before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject; and/or
(vii) a histology grade and a mean stage-adjusted score is to be determined before and after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject, wherein a decrease in the histology grade or the mean stage-adjusted score after administration of the 13C5.5 antibody, or antigen-binding portion thereof, to the subject as compared to the histology grade or the mean stage-adjusted score before administration indicates that the 13C5.5 antibody, or antigen-binding portion thereof, is effective in treating the subject.

22. The use of claim 21, wherein the dysphagia clinical symptoms of (ii) are assessed using the eosinophilic esophagitis activity index (EEsAI) and recorded as a daily symptom diary (DSD) score.

23. The use of claim 21, wherein the EREF of (iv) is determined based on the presence of inflammatory markers in the esophagus, the presence of remodeling markers in the esophagus, or a combination thereof.

24. The use of claim 21, wherein the EREF of (iv) is determined based on the presence or absence of plurality of features selected from the group consisting of edema, fixed rings, exudates, furrows and stricture, or a combination thereof.

25. The use of any one of claims 2-24, wherein an additional agent is to be further administered to the subject.

26. The use of claim 25, wherein the additional agent is a steroid.

27. The use of claim 26, wherein the steroid is budesonide.

28. The use of claim 25, wherein the additional agent is selected from the group consisting of: a therapeutic agent, an imaging agent, a cytotoxic agent, an angiogenesis inhibitor, a kinase inhibitor, a co-stimulation molecule blocker, an adhesion molecule blocker, an anti-cytokine antibody or functional fragment thereof; methotrexate, a cyclosporin, a rapamycin, an FK506, a detectable label or reporter, a TNF antagonist, an anti-rheumatic, a muscle relaxant, a narcotic, a non-steroid anti-inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anesthetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteroid, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an oral steroid, an epinephrine or analog, a cytokine, and a cytokine antagonist.