

to anti-IgE antibodies such as omalizumab. In autoimmune urticaria, affected patients produced IgG auto-antibodies against FcεRI, IgE, or both, which can cross-link IgE-occupied or unoccupied FcεRI to activate mast cells in the skin (see, e.g., Konstantinou, G.N. *et al.* (2013) *Allergy* 68:27-36 and Chang, T.W. *et al.* (2015) *J. Allergy Clin. Immunol.* 135:337-342).

[0009] Accordingly, in one aspect, the present disclosure refers to use of a composition comprising an antibody that binds to human Siglec-8 in the manufacture of a medicament for treating chronic urticaria in an individual; wherein, prior to administration of the composition, the urticaria in the individual is not adequately controlled, or urticaria symptoms remain, despite treatment with H1-antihistamine; wherein administration of the composition results in a decrease in UAS7 score of the individual of greater than 10; and wherein the antibody is a monoclonal antibody that comprises a heavy chain comprising a heavy chain variable region, and a light chain comprising a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:6, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NO:16 or 21. In another aspect, the present disclosure refers to use of a composition comprising an antibody that binds to human Siglec-8 in the manufacture of a medicament for treating chronic urticaria in an individual; wherein, prior to administration of the composition, the individual has demonstrated an inadequate response to treatment with an anti-IgE antibody or the urticaria in the individual is inadequately controlled by treatment with an anti-IgE antibody; wherein administration of the composition results in a decrease in UAS7 score of the individual of greater than 10; and wherein the antibody is a monoclonal antibody that comprises a heavy chain comprising a heavy chain variable region, and a light chain comprising a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:6, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NO:16 or 21.

[0009a] Certain examples of the present disclosure relate to methods for treating chronic urticaria in an individual comprising administering to the individual an effective amount of a composition comprising an antibody that binds to human Siglec-8, wherein the individual is resistant or refractory to treatment with H1-antihistamine. Other examples of the present disclosure relate to methods for treating chronic urticaria in an individual comprising administering to the individual an effective amount of an antibody that binds to human Siglec-8, wherein the individual is resistant or refractory to treatment with H1-antihistamine. Other examples of the present disclosure relate to methods for treating chronic urticaria in an individual comprising administering to the individual an effective amount of an antibody that binds to human Siglec-8, wherein the urticaria remains uncontrolled despite treatment with H1-antihistamine. Other examples of the present disclosure relate to methods for treating chronic urticaria in an individual comprising administering to the individual an effective amount of a composition comprising an antibody that binds to human Siglec-8; wherein, prior to administration of the composition, the urticaria in the individual is uncontrolled despite treatment with H1-antihistamine. Other examples of the present disclosure relate to methods for treating chronic urticaria in an individual comprising administering to the individual an effective amount of a composition comprising an antibody that binds to human Siglec-8; wherein, prior to administration of the composition, urticaria symptoms in the individual remain despite treatment with H1-antihistamine. Other examples of the present disclosure relate to methods for treating chronic urticaria in an individual comprising administering to the individual an effective amount of a composition comprising an antibody that binds to human Siglec-8; wherein, prior to administration of the composition, the individual remains symptomatic despite treatment with H1-antihistamine.

CLAIMS

What is claimed is:

1. Use of a composition comprising an antibody that binds to human Siglec-8 in the manufacture of a medicament for treating chronic urticaria in an individual; wherein, prior to administration of the composition, the urticaria in the individual is not adequately controlled, or urticaria symptoms remain, despite treatment with H1-antihistamine; wherein administration of the composition results in a decrease in UAS7 score of the individual of greater than 10; and wherein the antibody is a monoclonal antibody that comprises a heavy chain comprising a heavy chain variable region, and a light chain comprising a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:6, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NO:16 or 21.
2. The use of claim 1, wherein:
 - (a) the individual has demonstrated an inadequate response to treatment with an anti-IgE antibody or the chronic urticaria is inadequately controlled by treatment with an anti-IgE antibody; or
 - (b) prior to administration of the composition, the individual is anti-IgE antibody-naive; wherein optionally the anti-IgE antibody is omalizumab or ligelizumab.
3. Use of a composition comprising an antibody that binds to human Siglec-8 in the manufacture of a medicament for treating chronic urticaria in an individual; wherein, prior to administration of the composition, the individual has demonstrated an inadequate response to treatment with an anti-IgE antibody or the urticaria in the individual is inadequately controlled by treatment with an anti-IgE antibody; wherein administration of the composition results in a decrease in UAS7 score of the individual of greater than 10; and wherein the antibody is a monoclonal antibody that comprises a heavy chain comprising a heavy chain variable region, and a light chain comprising a light chain variable region, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:6, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NO:16 or 21.
4. The use of claim 3, wherein the anti-IgE antibody is omalizumab or ligelizumab.

5. The use of claim 3 or claim 4, wherein, prior to administration of the composition, the urticaria in the individual is uncontrolled despite treatment with H1-antihistamine.

6. The use of any one of claims 1, 2, and 5, wherein, prior to administration of the composition:

(a) the urticaria in the individual is uncontrolled despite treatment with H1-antihistamine at label dosage or four-fold label dosage; or

(b) the urticaria in the individual is uncontrolled despite treatment with H1-antihistamine at up to four-fold label dosage.

7. The use of any one of claims 1-6, wherein:

(a) the chronic urticaria is chronic cholinergic, dermatographic, cold-induced, vibratory, autoimmune, spontaneous, or idiopathic urticarial;

(b) the chronic urticaria is chronic autoimmune urticaria, and wherein the individual has demonstrated a positive result in one or more of the following tests before administration of the composition: basophil histamine release assay (BHRA), basophil activation marker expression, autologous serum skin test (ASST), and immunoassay for IgG autoantibodies against IgE and/or FcεRI; and/or

(c) the individual has demonstrated a UCT score of less than 12 before administration of the composition.

8. The use of any one of claims 1-7, wherein one or more symptom(s) in the individual with chronic urticaria are reduced after administration of the composition, as compared to a baseline level before administration of the composition; wherein optionally:

(a) self-assessed disease activity is reduced as compared to a baseline level before administration of the composition, wherein self-assessed disease activity is optionally assessed by one or more of the following metrics: UCT, UAS7, and CholUAS7;

(b) self-assessed quality-of-life score is improved as compared to a baseline level before administration of the composition, wherein self-assessed quality-of-life score is optionally

assessed by one or more of the following metrics: DLQI, CU-Q2oL, AE-QoL, SD-QoL, and CholU-QoL;

(c) one or more of the following are reduced as compared to a baseline level before administration of the composition: occurrence of angioedema, number of hives, and itch severity; or

(d) one or more of the following are increased as compared to a baseline level before administration of the composition: number of symptom-free days per week and trigger threshold.

9. The use of any one of claims 1-8, wherein number of eosinophils, total IgE, expression of tryptase, expression of eosinophil cationic protein, and/or number of basophils in a serum sample from the individual is reduced as compared to a baseline level in a serum sample obtained from the individual before administration of the composition.

~~10. —The use of any one of claims 1-9, wherein:~~

~~(a) administration of the composition results in a sustained response to treatment;~~

~~(b) administration of the composition results in a UCT score of 12 or above at 10 weeks after treatment;~~

~~(c) administration of the composition results in a UCT score of 12 or above at 22 weeks after treatment; or~~

~~(d) administration of the composition results in a decrease in UAS7 score of greater than 10.~~

~~11.10.~~ -The use of any one of claims 1-~~109~~, wherein the composition is to be administered by intravenous infusion, wherein optionally the composition is to be administered by intravenous infusion once a month for 3 or more months.

~~12.11.~~ The use of any one of claims 1-~~109~~, wherein the composition is to be administered by subcutaneous injection.

~~13.12.~~ The use of any one of claims 1-~~109~~, wherein the composition is to be administered by intravenous infusion at one or more doses comprising between ~~about~~ 0.3 mg/kg and ~~about~~ 3.0

mg/kg of the antibody; wherein optionally two or more doses comprising between ~~about~~ 0.3 mg/kg and ~~about~~ 3.0 mg/kg of the antibody are to be administered to the individual at an interval of ~~about~~ 28 days, ~~about~~ 4 weeks, or monthly; wherein optionally -to the individual is to be administered a first dose comprising ~~about~~ 0.3 mg/kg of the antibody, a second dose comprising ~~about~~ 1.0 mg/kg of the antibody, a third dose comprising ~~about~~ 1.0 mg/kg of the antibody, a fourth dose comprising ~~about~~ 1.0 mg/kg to ~~about~~ 3.0 mg/kg of the antibody, a fifth dose comprising ~~about~~ 1.0 mg/kg to ~~about~~ 3.0 mg/kg of the antibody, and a sixth dose comprising ~~about~~ 1.0 mg/kg to ~~about~~ 3.0 mg/kg of the antibody, wherein optionally the first dose is to be administered at Day 1, wherein the second dose is to be administered at Day 29, wherein the third dose is to be administered at Day 57, wherein the fourth dose is to be administered at Day 85, wherein the fifth dose is to be administered at Day 113, and wherein the sixth dose is to be administered at Day 141.

14.13. The use of any one of claims 1-~~13~~12, wherein the antibody comprises a Fc region and N-glycoside-linked carbohydrate chains linked to the Fc region, wherein less than 50% of the N-glycoside-linked carbohydrate chains of the antibody in the composition contain a fucose residue.

15.14. The use of claim ~~14~~13, wherein substantially none of the N-glycoside-linked carbohydrate chains of the antibody in the composition contain a fucose residue.

~~16. — The use of any one of claims 1–15, wherein the antibody comprises a heavy chain variable region and a light chain variable region, and wherein:~~

~~(a) the heavy chain variable region comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:61, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:62, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:63, and the light chain variable region comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:64, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:65, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:66;~~

~~(b) the heavy chain variable region comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:61, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:62, and (iii) HVR-H3 comprising the amino acid sequence selected from SEQ ID NOs:67–~~

70, and the light chain variable region comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:64, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:65, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:71;

(c) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:6, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:16 or 21;

(d) the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs:11-14, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs:23-24;

(e) the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs:2-14, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs:16-24;

(f) the heavy chain variable region comprises an amino acid sequence selected from SEQ ID NOs:2-10, and the light chain variable region comprises an amino acid sequence selected from SEQ ID NOs:16-22;

(g) the heavy chain variable region comprises an HC-FR1 comprising the amino acid sequence selected from SEQ ID NOs:26-29, an HVR-H1 comprising the amino acid sequence of SEQ ID NO:61, an HC-FR2 comprising the amino acid sequence selected from SEQ ID NOs:31-36, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62, an HC-FR3 comprising the amino acid sequence selected from SEQ ID NOs:38-43, an HVR-H3 comprising the amino acid sequence of SEQ ID NO:63, and an HC-FR4 comprising the amino acid sequence selected from SEQ ID NOs:45-46, and the light chain variable region comprises an LC-FR1 comprising the amino acid sequence selected from SEQ ID NOs:48-49, an HVR-L1 comprising the amino acid sequence of SEQ ID NO:64, an LC-FR2 comprising the amino acid sequence selected from SEQ ID NOs:51-53, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:65, an LC-FR3 comprising the amino acid sequence selected from SEQ ID NOs:55-58, an HVR-L3 comprising the amino acid sequence of SEQ ID NO:66, and an LC-FR4 comprising the amino acid sequence of SEQ ID NO:60;

(h) the heavy chain variable region comprises an HC-FR1 comprising the amino acid sequence of SEQ ID NO:26, an HVR-H1 comprising the amino acid sequence of SEQ ID

NO:61, an HC-FR2 comprising the amino acid sequence of SEQ ID NO:34, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62, an HC-FR3 comprising the amino acid sequence of SEQ ID NO:38, an HVR-H3 comprising the amino acid sequence of SEQ ID NO:63, and an HC-FR4 comprising the amino acid sequence of SEQ ID NO:45, and the light chain variable region comprises an LC-FR1 comprising the amino acid sequence of SEQ ID NO:48, an HVR-L1 comprising the amino acid sequence of SEQ ID NO:64, an LC-FR2 comprising the amino acid sequence of SEQ ID NO:51, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:65, an LC-FR3 comprising the amino acid sequence of SEQ ID NO:55, an HVR-L3 comprising the amino acid sequence of SEQ ID NO:66, and an LC-FR4 comprising the amino acid sequence of SEQ ID NO:60;

(i) the heavy chain variable region comprises an HC-FR1 comprising the amino acid sequence of SEQ ID NO:26, an HVR-H1 comprising the amino acid sequence of SEQ ID NO:61, an HC-FR2 comprising the amino acid sequence of SEQ ID NO:34, an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62, an HC-FR3 comprising the amino acid sequence of SEQ ID NO:38, an HVR-H3 comprising the amino acid sequence of SEQ ID NO:63, and an HC-FR4 comprising the amino acid sequence of SEQ ID NO:45, and the light chain variable region comprises an LC-FR1 comprising the amino acid sequence of SEQ ID NO:48, an HVR-L1 comprising the amino acid sequence of SEQ ID NO:64, an LC-FR2 comprising the amino acid sequence of SEQ ID NO:51, an HVR-L2 comprising the amino acid sequence of SEQ ID NO:65, an LC-FR3 comprising the amino acid sequence of SEQ ID NO:58, an HVR-L3 comprising the amino acid sequence of SEQ ID NO:66, and an LC-FR4 comprising the amino acid sequence of SEQ ID NO:60;

—— (j) the heavy chain variable region comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:88, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:91, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:94, and the light chain variable region comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:97, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:100, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:103;

—— (k) the heavy chain variable region comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:89, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:92, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:95, and the light chain variable region comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID

NO:98, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:101, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:104;

~~(l) the heavy chain variable region comprises (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO:90, (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO:93, and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO:96, and the light chain variable region comprises (i) HVR-L1 comprising the amino acid sequence of SEQ ID NO:99, (ii) HVR-L2 comprising the amino acid sequence of SEQ ID NO:102, and (iii) HVR-L3 comprising the amino acid sequence of SEQ ID NO:105;~~

~~——(m) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:106, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:109;~~

~~——(n) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:107, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:110; or~~

~~——(o) the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:108, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:111.~~

17. —The use of any one of claims 1-15, wherein the antibody binds to a human Siglec-8 and a non-human primate Siglec-8.

18. —The use of any one of claims 1-15, wherein the antibody binds to an epitope in Domain 2 or Domain 3 of human Siglec-8.

19. —The use of any one of claims 1-15, wherein the antibody binds to an epitope in Domain 1 of human Siglec-8 and competes with antibody 4F11 for binding to Siglec-8.

20. —The use of any one of claims 16-19, wherein the antibody is a human antibody, a humanized antibody, or a chimeric antibody.

21. —The use of any one of claims 16-20, wherein the antibody depletes blood eosinophils and inhibits mast cell activation.

22.15. The use of any one of claims 1-~~21~~14, wherein the antibody comprises a heavy chain Fc region comprising a human IgG Fc region.

23.16. The use of claim 2215, wherein the human IgG Fc region comprises a human IgG1 Fc region, wherein optionally the human IgG1 Fc region is non-fucosylated or has reduced fucosylation.

24.17. The use of claim 2215, wherein the human IgG Fc region comprises a human IgG4 Fc region, wherein optionally the human IgG4 Fc region comprises the amino acid substitution S228P, wherein the amino acid residues are numbered according to the EU index as in Kabat.

25.18. The use of any one of claims 1-2417, wherein the antibody has been engineered to improve antibody-dependent cell-mediated cytotoxicity (ADCC) activity, wherein optionally the antibody comprises at least one amino acid substitution in the Fc region that improves ADCC activity.

26.19. The use of any one of claims 1-2418, wherein at least one or two of the heavy chains of the antibody is non-fucosylated.

27.20. The use of any one of claims 1-4514, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:75; and ~~for~~ a light chain comprising the amino acid sequence selected from SEQ ID NO:76 or 77.

~~28. — The use of any one of claims 1-27, wherein the antibody is a monoclonal antibody.~~

29.21. The use of any one of claims 1-2820, wherein the composition is to be administered in combination with one or more additional therapeutic agent(s) for treating or preventing chronic urticarial, wherein optionally the one or more additional therapeutic agent(s) for treating or preventing chronic urticaria are selected from the group consisting of H-2 receptor antagonists, H1-antihistamines, H2-antihistamines, anti-IgE antibodies, corticosteroids, doxepin, leukotriene receptor antagonists (LTRAs), cyclosporine, and tacrolimus.

30.22. The use of any one of claims 1-2921, wherein the individual is a human.

31.23. The use of any one of claims 1-3022, wherein the treatment results in:

(a) a complete response in the individual after a single administration of the composition;

(b) at least a 3-point improvement in UCT score in the individual, as compared to UCT score in the individual prior to treatment;

(c) a reduction in UAS7 score of at least 50% in the individual, as compared to UAS7 score in the individual prior to treatment; or

(d) a reduction in UAS7 score by at least 10 in the individual, as compared to UAS7 score in the individual prior to treatment.

32.24. The use of any one of claims 1-~~31~~23, wherein the composition comprises the antibody and a pharmaceutically acceptable carrier.