

[0005] Many urticaria patients are adequately treated by current therapies such as high dose antihistamines. The most common form of chronic urticaria is chronic spontaneous or idiopathic urticaria. This subtype is believed to be an allergic disease in which IgE plays an important role. Omalizumab (sold as XOLAIR®) is an anti-IgE antibody approved for use in chronic spontaneous urticaria that cannot be managed with H1-antihistamines alone, even at higher than approved doses. However, some patients have demonstrated resistance to omalizumab (*see, e.g., Metz, M. et al. (2014) J. Dermatol. Sci. 73:57-62*). The response rate to omalizumab in chronic spontaneous urticaria ranges from 55% to 70-80% when higher than approved doses are used. In the case of physical urticarias, the response rates are lower. In particular, Metz *et al.* described that the response rate to omalizumab in patients with cholinergic urticaria was low, with only 5/8 patients with cholinergic urticaria showing a complete response to omalizumab (as compared to 25/30 for chronic spontaneous urticaria).

[0006] Currently, there is no biologic treatment approved for use in inducible urticarias. A significant number of patients do not receive adequate benefit from current therapies such as H1-antihistamine and/or anti-IgE treatment, and their uncontrolled urticaria symptoms can have a significant impact on quality of life. As such, there remains a need for novel therapeutic approaches that target the inflammation underlying chronic urticarias.

[0007] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0008] To meet this and other needs, the present disclosure relates, *inter alia*, to methods of treating or preventing chronic urticaria by administration of antibodies that bind to human Siglec-8 and/or compositions comprising said antibodies. In particular, and due in part to their unique mechanism of action, the methods and compositions described herein may find use in treating individuals that are resistant or refractory to treatment with H1-antihistamine and/or anti-IgE antibody, those with urticaria that is not adequately controlled or urticaria symptoms that remains despite treatment with H1-antihistamine, those that have relapsed after treatment with an anti-IgE antibody, those that have demonstrated an inadequate response to treatment with an anti-IgE antibody, or those whose urticaria symptoms are inadequately controlled by treatment with an anti-IgE antibody. Without wishing to be bound to theory, it is thought that anti-Siglec-8 antibody can inhibit mast cell responses to autoantibodies, *e.g.,* in patients resistant

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. 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.

[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, the urticaria in the individual is not adequately controlled 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.

[0010] 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 the individual is resistant or refractory to treatment with an anti-IgE antibody or has relapsed after treatment with an anti-IgE antibody. 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 an anti-IgE antibody or has relapsed after treatment with an anti-IgE antibody. 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 has demonstrated an inadequate response to treatment with an anti-IgE antibody or the urticaria is inadequately controlled by treatment with an anti-IgE antibody. 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 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. 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 not adequately controlled despite treatment with an anti-IgE antibody. 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 an anti-IgE antibody. 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 an anti-IgE antibody.

[0011] Other examples of the present disclosure relate to methods for decreasing UAS7 score in an individual having chronic urticaria, comprising administering to the individual an effective

amount of a composition comprising an antibody that binds to human Siglec-8; wherein administration of the composition results in a decrease in UAS7 score by 10 or greater, *e.g.*, as compared to a baseline UAS7 score in the individual prior to treatment. In some examples, prior to administration of the composition, the individual remains symptomatic or has urticaria that is inadequately controlled despite treatment with H1-antihistamine (*e.g.*, at single or up to four-fold dosage). In some examples, prior to administration of the composition, the individual remains symptomatic or has urticaria that is inadequately controlled despite treatment with anti-IgE antibody.

[0012] In some examples, the individual is resistant or refractory to treatment with an anti-IgE antibody. In some examples, the individual has relapsed after treatment with an anti-IgE antibody. In some examples, the individual has demonstrated an inadequate response to treatment with an anti-IgE antibody or the urticaria is inadequately controlled by treatment with an anti-IgE antibody. In some examples, prior to administration of the composition, the individual is anti-IgE antibody-naïve. In some examples, the individual has not been treated with an anti-IgE antibody prior to administration of composition or the antibody that binds to human Siglec-8. In some examples, the individual has not been treated with an anti-IgE antibody for at least 2 months prior to administration of composition or the antibody that binds to human Siglec-8. In some examples, the individual has not been treated with an anti-IgE antibody for at least 3 months prior to administration of composition or the antibody that binds to human Siglec-8. In some examples, the anti-IgE antibody is omalizumab. In some examples, the anti-IgE antibody is ligelizumab.

[0013] In some examples, the individual is resistant or refractory to treatment with H1-antihistamine. In some examples, the individual remains symptomatic despite prior treatment with H1-antihistamine. In some examples, prior to administration of the composition, the urticaria in the individual is uncontrolled despite treatment with H1-antihistamine. In some examples, the individual is resistant or refractory to treatment with H1-antihistamine at single or label dosage. In some examples, the individual remains symptomatic despite prior treatment with H1-antihistamine at single or label dosage. In some examples, the individual is resistant or refractory to treatment with H1-antihistamine at four-fold dosage. In some examples, the individual remains symptomatic despite treatment with H1-antihistamine at up to four-fold label dosage. In some examples, the individual remains symptomatic despite prior treatment with H1-antihistamine at up to four-fold label dosage. In

some examples, an individual with uncontrolled urticaria reports a UCT score of less than 12, *e.g.*, despite treatment with H1-antihistamine (*e.g.*, at single or four-fold dosage).

[0014] In some examples, the individual is resistant or refractory to treatment with H1-antihistamine and is resistant or refractory to treatment with an anti-IgE antibody. In some examples, the individual is resistant or refractory to treatment with H1-antihistamine at single label dosage or up to four-fold label dosage and is resistant or refractory to treatment with an anti-IgE antibody. In some examples, the individual remains symptomatic despite prior treatment with H1-antihistamine and treatment with an anti-IgE antibody. In some examples, the individual has demonstrated an inadequate response to treatment with an anti-IgE antibody and treatment with H1-antihistamine (*e.g.*, at single or four-fold dosage) or the urticaria is inadequately controlled by treatment with an anti-IgE antibody and treatment with H1-antihistamine (*e.g.*, at single or four-fold dosage).

[0015] In some examples, the individual has or has been diagnosed with a chronic urticaria. In some examples, the chronic urticaria is a chronic inducible urticaria. In some examples, the chronic urticaria is a chronic spontaneous urticaria. In some examples, the chronic urticaria is chronic cholinergic, dermatographic or urticaria factitia, cold-induced, vibratory, autoimmune, or idiopathic urticaria. In some examples, the chronic urticaria is symptomatic dermographism, chronic cholinergic, dermatographic, heat-induced, aquagenic, solar-induced, pressure- or contact-induced, cold-induced, vibratory, autoimmune, or idiopathic urticaria. In some examples, the chronic urticaria is a chronic inducible urticaria of multiple types. In some examples, the chronic urticaria is chronic cholinergic urticaria. In some examples, the chronic urticaria is chronic dermatographic urticaria or symptomatic dermographism. In some examples, 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. In some examples, the individual has demonstrated a UCT score of less than 12 before administration of the composition. In some examples, one or more symptom(s) in the individual with chronic urticaria are reduced as compared to a baseline level before administration of the composition. In some examples, self-assessed disease activity is reduced as compared to a baseline level before administration of the composition. In some examples, self-assessed disease activity is assessed by one or

more of the following metrics: UCT, UAS7, and CholUAS7. In some examples, self-assessed quality-of-life score is improved as compared to a baseline level before administration of the composition. In some examples, self-assessed quality-of-life score is assessed by one or more of the following metrics: DLQI, CU-Q2oL, AE-QoL, SD-QoL, and CholU-QoL. In some examples, 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. In some examples, 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. In some examples, administration of the composition results in a sustained response to treatment. In some examples, administration of the composition results in a decrease in UAS7 score of greater than 10. In some examples, administration of the composition results in a UCT score of 12 or above at 10 weeks after treatment. In some examples, administration of the composition results in a UCT score of 12 or above, 13 or above, or 14 or above at week 22 of treatment. In some examples, administration of the composition results in a mean increase in UCT score of about 11, or a mean increase in UCT score of about 400%. In some examples, administration of the composition results in a complete response to treatment. In some examples, a complete response to treatment refers to an improvement of 3 or more in UCT score and a UCT score of greater than 12. In some examples, administration of the composition results in a partial response to treatment. In some examples, a partial response to treatment refers to an improvement of 3 or more in UCT score. In some examples, the composition is administered by intravenous infusion. In some examples, the composition is administered by intravenous infusion once a month for 3 or more months. In some examples, the composition is administered by subcutaneous injection. In some examples, the composition is 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. In some examples, two or more doses comprising between about 0.3 mg/kg and about 3.0 mg/kg of the antibody are administered to the individual at an interval of about 28 days, about 4 weeks, or monthly. In some examples, the method comprises administering to the individual 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. In some examples, the first dose is administered at Day 1, wherein the second dose is administered at Day 29, wherein the third dose is administered at Day 57, wherein the fourth dose is administered at Day 85, wherein the fifth dose is administered at Day 113, and wherein the sixth dose is administered at Day 141. In some examples, treatment with the antibody that binds to human Siglec-8 leads to a greater reduction in one or more urticaria symptoms (*e.g.*, as measured by UAS7 and/or UCT score), as compared to treatment with an anti-IgE antibody (*e.g.*, omalizumab or ligelizumab). In some examples, the individual has a UAS7 score of 16 or greater prior to treatment with an antibody that binds to human Siglec-8, and treatment with an antibody that binds to human Siglec-8 leads to a greater reduction in UAS7 score, as compared to treatment with an anti-IgE antibody (*e.g.*, omalizumab or ligelizumab). In some examples, administration of the composition results in a UAS7 score of 4 or below at week 22 of treatment. In some examples, administration of the composition results in a mean reduction in UAS7 score of about 14, or a mean reduction in UAS7 score of about 75%.

[0016] In some examples, 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. In some examples, substantially none of the N-glycoside-linked carbohydrate chains of the antibody in the composition contain a fucose residue. In some examples, the antibody comprises a heavy chain variable region and a light chain variable region, wherein 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/or wherein 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. In some examples, the antibody comprises a heavy chain variable region and a light chain variable region, wherein 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/or wherein 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. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:6; and/or a light chain variable region comprising the amino acid sequence selected from SEQ ID NO:16 or 21. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence selected from SEQ ID NOs:11-14; and/or a light chain variable region comprising the amino acid sequence selected from SEQ ID NOs:23-24. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence selected from SEQ ID NOs:2-14; and/or a light chain variable region comprising the amino acid sequence selected from SEQ ID NOs:16-24. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence selected from SEQ ID NOs:2-10; and/or a light chain variable region comprising the amino acid sequence selected from SEQ ID NOs:16-22. In some examples, the antibody comprises: (a) heavy chain variable region comprising: (1) an HC-FR1 comprising the amino acid sequence selected from SEQ ID NOs:26-29; (2) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:61; (3) an HC-FR2 comprising the amino acid sequence selected from SEQ ID NOs:31-36; (4) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62; (5) an HC-FR3 comprising the amino acid sequence selected from SEQ ID NOs:38-43; (6) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:63; and (7) an HC-FR4 comprising the amino acid sequence selected from SEQ ID NOs:45-46, and/or (b) a light chain variable region comprising: (1) an LC-FR1 comprising the amino acid sequence selected from SEQ ID NOs:48-49; (2) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:64; (3) an LC-FR2 comprising the amino acid sequence selected from SEQ ID NOs:51-53; (4) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:65; (5) an LC-FR3 comprising the amino acid sequence selected from SEQ ID NOs:55-58; (6) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:66; and (7) an LC-FR4 comprising the amino acid sequence of SEQ ID NO:60. In some examples, the antibody comprises: (a) heavy chain variable region comprising: (1) an HC-FR1 comprising the amino acid sequence of SEQ ID NO:26; (2) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:61; (3) an HC-FR2 comprising the amino acid sequence of SEQ ID NO:34; (4) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62; (5) an HC-FR3 comprising the amino acid sequence of SEQ ID NO:38; (6) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:63; and (7)

an HC-FR4 comprising the amino acid sequence of SEQ ID NOs:45; and/or (b) a light chain variable region comprising: (1) an LC-FR1 comprising the amino acid sequence of SEQ ID NO:48; (2) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:64; (3) an LC-FR2 comprising the amino acid sequence of SEQ ID NO:51; (4) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:65; (5) an LC-FR3 comprising the amino acid sequence of SEQ ID NO:55; (6) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:66; and (7) an LC-FR4 comprising the amino acid sequence of SEQ ID NO:60. In some examples, the antibody comprises: (a) heavy chain variable region comprising: (1) an HC-FR1 comprising the amino acid sequence of SEQ ID NO:26; (2) an HVR-H1 comprising the amino acid sequence of SEQ ID NO:61; (3) an HC-FR2 comprising the amino acid sequence of SEQ ID NO:34; (4) an HVR-H2 comprising the amino acid sequence of SEQ ID NO:62; (5) an HC-FR3 comprising the amino acid sequence of SEQ ID NO:38; (6) an HVR-H3 comprising the amino acid sequence of SEQ ID NO:63; and (7) an HC-FR4 comprising the amino acid sequence of SEQ ID NOs:45; and/or (b) a light chain variable region comprising: (1) an LC-FR1 comprising the amino acid sequence of SEQ ID NO:48; (2) an HVR-L1 comprising the amino acid sequence of SEQ ID NO:64; (3) an LC-FR2 comprising the amino acid sequence of SEQ ID NO:51; (4) an HVR-L2 comprising the amino acid sequence of SEQ ID NO:65; (5) an LC-FR3 comprising the amino acid sequence of SEQ ID NO:58; (6) an HVR-L3 comprising the amino acid sequence of SEQ ID NO:66; and (7) an LC-FR4 comprising the amino acid sequence of SEQ ID NO:60. In some examples, the antibody comprises: a heavy chain variable region comprising (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/or a light chain variable region comprising (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; a heavy chain variable region comprising (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/or a light chain variable region comprising (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; or a heavy chain variable region comprising (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/or a light chain variable region comprising (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. In some examples, the antibody comprises: a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:106; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO:109; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:107; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO:110; or a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:108; and/or a light chain variable region comprising the amino acid sequence of SEQ ID NO:111. In some examples, the antibody binds to a human Siglec-8 and a non-human primate Siglec-8. In some examples, the non-human primate is a baboon. In some examples, the antibody binds to an epitope in Domain 1 of human Siglec-8, wherein Domain 1 comprises the amino acid sequence of SEQ ID NO:112. In some examples, the antibody binds to an epitope in Domain 3 of human Siglec-8, wherein Domain 3 comprises the amino acid sequence of SEQ ID NO:114. In some examples, the antibody binds to the same epitope as antibody 4F11. In some examples, the antibody binds to an epitope in Domain 2 or Domain 3 of human Siglec-8. In some examples, Domain 2 comprises the amino acid sequence of SEQ ID NO:113. In some examples, the antibody binds to the same epitope as antibody 1C3. In some examples, Domain 3 comprises the amino acid sequence of SEQ ID NO:114. In some examples, the antibody binds to the same epitope as antibody 1H10. In some examples, the antibody binds to an epitope in Domain 1 of human Siglec-8 and competes with antibody 4F11 for binding to Siglec-8. In some examples, the antibody does not compete with antibody 2E2 for binding to Siglec-8. In some examples, the antibody is not antibody 2E2. In some examples, Domain 1 comprises the amino acid sequence of SEQ ID NO:112. In some examples, the antibody is a human antibody, a humanized antibody, or a chimeric antibody. In some examples, the antibody comprises a heavy chain Fc region comprising a human IgG Fc region. In some examples, the human IgG Fc region comprises a human IgG1 Fc region. In some examples, the human IgG1 Fc region is non-fucosylated. In some examples, the human IgG Fc region comprises a human IgG4 Fc region. In some examples, 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. In some

examples, the antibody depletes blood eosinophils and/or inhibits mast cell activation. In some examples, the antibody has been engineered to improve antibody-dependent cell-mediated cytotoxicity (ADCC) activity. In some examples, the antibody comprises at least one amino acid substitution in the Fc region that improves ADCC activity. In some examples, the antibody has reduced fucosylation as compared to a wild type IgG1. In some examples, at least one or two of the heavy chains of the antibody is non-fucosylated. In some examples, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:75; and/or a light chain comprising the amino acid sequence selected from SEQ ID NO:76 or 77. In some examples, the anti-Siglec-8 antibody that is used in the methods described herein has a human IgG1 and has reduced fucosylation as compared to a wild type human IgG1. In some examples, one or two of the heavy chains of the antibody is non-fucosylated. In some examples, the antibody is produced in a mammalian cell line having an alpha1,6-fucosyltransferase (Fut8) knockout. In some examples, the antibody is produced in a cell line overexpressing beta 1, 4-N-acetylglucosaminyltransferase III (GnT-III). In some examples, the cell line additionally overexpresses Golgi μ -mannosidase II (ManII). In some examples, the cell line is a CHO cell line. In some examples, the antibody is a monoclonal antibody.

[0017] In some examples, the composition or antibody is administered in combination with one or more additional therapeutic agent(s) for treating or preventing chronic urticaria. In some examples, 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.

[0018] In some examples, the individual is a human. In some examples, the treatment results in a complete response in the individual after cessation of the treatment. In some examples, 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. In some examples, the treatment results in a complete response in the individual after a single administration of the composition. In some examples, the treatment results in at least a 3-point improvement in UCT score in the individual, as compared to UCT score in the individual prior to treatment. In some examples, the treatment results in a

reduction in UAS7 score of at least 50% in the individual, as compared to UAS7 score in the individual prior to treatment.

[0019] In some examples, the composition comprises the antibody and a pharmaceutically acceptable carrier.

[0020] Other examples of the present disclosure relate to articles of manufacture or kits comprising a medicament comprising a composition comprising an antibody that binds to human Siglec-8 and a package insert comprising instructions for administration of the medicament in an individual in need thereof according to any one of the above examples. Other examples of the present disclosure relate to articles of manufacture or kits comprising a medicament comprising an antibody that binds to human Siglec-8 and a package insert comprising instructions for administration of the medicament in an individual in need thereof according to any one of the above examples.

[0021] Other examples of the present disclosure relate to a composition comprising an antibody that binds to human Siglec-8 for use in a method of treating chronic urticaria in an individual according to any one of the above examples. In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:6; and/or a light chain variable region comprising the amino acid sequence selected from SEQ ID NO:16 or 21. In some examples, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:75; and/or a light chain comprising the amino acid sequence selected from SEQ ID NO:76 or 77. In some examples, at least one or two of the heavy chains of the antibody is non-fucosylated.

[0022] It is to be understood that one, some, or all of the properties of the various examples described herein may be combined to form other examples of the present disclosure. These and other aspects of the present disclosure will become apparent to one of skill in the art. These and other examples of the present disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **FIG. 1A** illustrates the UCT and UAS7 measurement tools for assessing urticaria symptoms. Adapted from EAACI Urticaria guidelines as published in Zuberbier *et al.* (2018) *Allergy* 73:1393-1414.

[0024] **FIG. 1B** shows the effect of anti-Siglec-8 antibody treatment on mean UCT score in anti-IgE-naïve patients with chronic urticaria.

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.
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.
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. The use of any one of claims 1-10, 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. The use of any one of claims 1-10, wherein the composition is to be administered by subcutaneous injection.

13. The use of any one of claims 1-10, 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. The use of any one of claims 1-13, 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. The use of claim 14, 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. The use of any one of claims 1-21, wherein the antibody comprises a heavy chain Fc region comprising a human IgG Fc region.

23. The use of claim 22, 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. The use of claim 22, 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. The use of any one of claims 1-24, 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. The use of any one of claims 1-21, wherein at least one or two of the heavy chains of the antibody is non-fucosylated.
27. The use of any one of claims 1-15, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:75; and/or 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. The use of any one of claims 1-28, 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. The use of any one of claims 1-29, wherein the individual is a human.
31. The use of any one of claims 1-30, 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. The use of any one of claims 1-31, wherein the composition comprises the antibody and a pharmaceutically acceptable carrier.