

COMPOSITIONS AND METHODS FOR DEPLETION OF MAST CELLS**RELATED APPLICATIONS**

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/543,215 filed on October 9, 2023, U.S. Provisional Patent Application No. 63/555,780 filed on February 20, 2024, U.S. Provisional Patent Application No. 63/645,821 filed on May 10, 2024, U.S. Provisional Patent Application No. 63/649,158 filed on May 17, 2024, U.S. Provisional Patent Application No. 63/659,296 filed on June 12, 2024, U.S. Provisional Patent Application No. 63/543,245 filed on October 9, 2023, U.S. Provisional Patent Application No. 63/556,342 filed on February 21, 2024, U.S. Provisional Patent Application No. 63/645,820 filed on May 10, 2024, U.S. Provisional Patent Application No. 63/649,229 filed on May 17, 2024, U.S. Provisional Patent Application No. 63/659,293 filed on June 12, 2024, AND U.S. Provisional Patent Application No. 63/604,178 filed on November 29, 2023, each of which is incorporated herein by reference in its entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (JATH_017_05WO_SeqList_ST26.xml; Size: 43,800 bytes; and Date of Creation: October 7, 2024) is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present disclosure relates to compositions and methods for regulating mast cell activity, e.g., to reduce the release of histamine by activated mast cells. The compositions and methods described herein may be used to treat patients with mast cell-related diseases or disorders, including but not limited to chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU).

BACKGROUND

[0004] Mast cells are immune cells that play a key role in the inflammatory response to pathogens or injury and are typically found in the skin, lungs, digestive track, conjunctiva of the eye and the mucosal linings of the mouth and nose. Typically, mast cells are triggered by a specific antigen or antibody interaction to release histamine, a variety of cytokines, and other chemical mediators in order fight a potential infection and to recruit additional types of immune cells to aid in the body's response. However, with certain diseases, such as, e.g., CSU, CIndU,

allergic asthma, prurigo nodularis, and eosinophilic esophagitis, the mast cell response is dysregulated and may lead to unwanted responses such as hives, airway constriction or conjunctivitis.

[0005] Current therapeutic approaches to controlling mast cell response include the use of anti-histamines to counteract the release of histamine by activated mast cells, and anti-IgE antibody therapy to try to eliminate the antibodies responsible for triggering mast cell activation. However, some patients do not respond to H1-antihistamines. Treatment alternatives for H1-antihistamine refractory CSU participants include immunosuppressive agents such as cyclosporine A, or repeated exposure to oral glucocorticoids. There are potential significant adverse effects associated with both alternatives (e.g., high blood pressure, increased risk of infection, acne, increased risk of diabetes and osteoporosis, nephrotoxicity, hepatotoxicity, fatigue, depression).

[0006] Accordingly, there is a need in the art for additional therapies for controlling mast cell response and treating diseases and disorders associated with mast cells, such as CSU and CIndU.

BRIEF SUMMARY OF THE INVENTION

[0007] The present disclosure provides *inter alia* methods for treating mast cell-related diseases and disorders, e.g., by administering anti-c-kit antibodies or antigen-binding fragments thereof to a subject in need thereof.

[0008] In one aspect, the disclosure provides a method of depleting mast cells in a subject, comprising administering to the subject an anti-c-kit antibody, e.g., JSP191, or an antigen-binding fragment thereof, e.g., a (Fab')₂, e.g., a JSP191 (Fab')₂, wherein the method results in a decrease in the amount of mast cells in a subject, e.g., immediately following the administration of the antibody or antigen-binding fragment thereof, or at about one day, two days, three days, four days, five days, six days, ten days, one week, two weeks, one month, two months, four months, or six months following the administration of the antibody or antigen-binding fragment thereof. In certain embodiments, the method comprises administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit IgG antibody, e.g., JSP191, wherein each dose comprises about 40 mg to about 360 mg, about 50 mg to about 300 mg, or about 120 mg to about 180 mg of the anti-c-kit antibody. In certain embodiments, the method results in a decrease in the amount of mast cells in a subject, e.g., immediately following the conclusion of treatment, or at about one day, two days, three days, four days, five days, six days, ten days, one week, two weeks, one month, two months, four months, or six

months following the conclusion of treatment. In certain embodiments, the method selectively depletes mast cells as opposed to HSPCs from the subject.

[0009] In a related aspect, the disclosure provides a method of treating a mast cell-related disease or disorder in a subject, the method comprising administering to the subject one or more therapeutically effective doses of an anti-c-kit antibody, e.g., JSP191, or an antigen-binding fragment thereof, e.g., a F(ab')₂. In some embodiments, the subject has not responded to treatment with antihistamines or has not responded to or cannot tolerate omalizumab. In particular embodiments, the mast cell-related disease or disorder is selected from the group consisting of: urticarias, optionally chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), chronic idiopathic urticaria (CIU), or urticaria pigmentosa, prurigo nodularis, esophagitis, optionally eosinophilic esophagitis, asthma, allergic diseases and disorders, optionally allergic asthma, anaphylaxis, mastocytosis, mast cell activation syndrome (MCAS), fibrosis, dermatitis, atherosclerosis, endometriosis, interstitial cystitis and inflammatory bowel disease. In one embodiment, the method comprises administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit IgG antibody, e.g., JSP191, wherein each dose comprises about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody. In certain embodiments, the subject is administered a single dose of about 1 mg/kg body weight to about 4 mg/kg body weight. In certain embodiments, the method selectively depletes mast cells as opposed to HSPCs from the subject.

[0010] In particular embodiments, provided is a method for treating a mast cell-mediated disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of an anti-CD117 antibody or fragment thereof, wherein the anti-CD117 antibody comprises the heavy chain variable region of JSP191 and the light chain variable region of JSP191. In some embodiments, the subject has not responded to treatment with antihistamines or has not responded to or cannot tolerate omalizumab. In some embodiments, the mast cell-mediated disease or disorder is selected from the group consisting of urticarias, optionally chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), chronic idiopathic urticaria (CIU), or urticaria pigmentosa, prurigo nodularis, esophagitis, optionally eosinophilic esophagitis, asthma, allergic diseases and disorders, optionally allergic asthma, anaphylaxis, mastocytosis, mast cell activation syndrome (MCAS), fibrosis, dermatitis, atherosclerosis, endometriosis, interstitial cystitis and inflammatory bowel disease. In certain embodiments, the disease or disorder is selected from a urticaria, asthma, prurigo nodularis (PN), eosinophilic esophagitis (EoE), mastocytosis, urticaria pigmentosa, anaphylaxis,

endometriosis, interstitial cystitis, and mast cell activation syndrome (MCAS). In some embodiments, the mast cell-mediated disease or disorder is chronic urticaria. In some embodiments, the chronic urticaria is chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIndU). In some embodiments, the administration is about once every 2-12 weeks. In some embodiments, the administration is about once every 4-8 weeks. In some embodiments, the anti-CD117 antibody or fragment thereof is administered at a dose of 0.8 mg/kg to 5 mg/kg. In some embodiments, the anti-CD117 antibody or fragment thereof is administered at a dose of 1 mg/kg to 2 mg/kg. In some embodiments, the anti-CD117 antibody or fragment thereof is administered at a dose of 1.2 mg/kg to 1.8 mg/kg. In some embodiments, the administration is subcutaneous, intravenous, or intramuscular injection. In a particular embodiment, the administration is subcutaneous. In some embodiments, a first dose of the administration results in mast cell count reduction in the subject for at least one week, at least two weeks, at least three weeks, or at least four weeks. In some embodiments, the anti-CD117 antibody or fragment thereof comprises an IgG Fc fragment not capable of activating antibody-dependent cellular cytotoxicity (ADCC). In some embodiments, the antibody is JSP191.

[0011] In certain embodiments of any of the methods disclosed herein, the subject is administered two or more doses of the anti-c-kit antibody, which may be the same or different amounts of the anti-c-kit antibody. In particular embodiments, each of the doses is administered between eight weeks to one year apart, between eight weeks to six months apart, between eight weeks to four months apart, between twelve weeks to one year apart, between twelve weeks to six months apart, between twelve weeks and four months apart, about 8 weeks apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, about six months apart, eight months apart, about ten months apart, or about one year apart, optionally wherein the time interval between each dose varies. In certain embodiments, the interval of time between doses is about two weeks to about 24 weeks, about four weeks to about 16 weeks, about eight weeks to about 12 weeks, about two months to about six months, about 1 month to about six months, about two months to about four months, or about two months to about three months. In certain embodiments, the interval of time between doses is at least four weeks, at least six weeks or at least eight weeks. In certain embodiments, the interval of time between doses is up to six months. In certain embodiments, the subject is administered two or more doses of the antibody or antigen-binding fragment thereof. In certain embodiments, one of the two or more doses is administered every two weeks to six months, every four weeks to four months, every two to 16 weeks, every four to twelve weeks, every six to ten weeks, every seven

to 9 weeks, about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, or about every 12 weeks, optionally wherein the time interval between each dose varies. In certain embodiments, the interval of time between doses is about two weeks to about 24 weeks, about four weeks to about 16 weeks, about eight weeks to about 12 weeks, about two months to about six months, about 1 month to about six months, about two months to about four months, or about two months to about three months. In certain embodiments, the interval of time between doses is at least four weeks, at least six weeks or at least eight weeks. In certain embodiments, the interval of time between doses is up to six months.

[0012] In certain embodiments, a subject is administered a single, high dose of the anti-CD117 antibody (e.g., a JSP191) or antigen-binding fragment thereof (e.g., a JSP191 (Fab')₂). In particular embodiments, the single, high dose is about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.5 mg/kg, mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the single, high dose is about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In some embodiments, the method results in a $UAS7 \leq 6$ or a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90%.

[0013] In certain embodiments of any of the methods disclosed herein, the subject is administered one or more dose (e.g., intravenously or subcutaneously) of about 14.5 mg to about 200 mg, about 20 mg to about 500 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 50 mg to about 150 mg, about 50 mg to about 100 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 60 mg to about 150 mg, about 60 mg to about 100 mg, about 70 mg to about 300 mg, about 70 mg to about 200 mg, about 70 mg to about 150 mg, about 70 mg to about 100 mg of the antibody or antigen-binding fragment thereof, optionally about 14.5 mg to about 175 mg, about 20 mg to about 150 mg, about 25 mg to about 250 mg, about 35 mg to about 240 mg, about 35 mg to about 180 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about

240 mg, about 260 mg, about 280 mg, about 300 mg, of the anti-c-kit antibody, optionally wherein the disease or disorder is a mast cell disease or disorder. In certain embodiments, the subject is administered a dose of about 25 mg, about 30 mg, about 35 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 130 mg, about 150 mg, about 180 mg, about 200 mg, about 150 mg, about 175 mg, about 240 mg, about 280 mg, or about 300 mg of the antibody or antigen-binding fragment thereof. In particular embodiments, the subject is administered one or more dose of an anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191, wherein each dose is between 40 mg and 360 mg or 120 mg and 240 mg, and each dose is administered subcutaneously between about eight weeks to about six months apart.

[0014] In certain embodiments of any of the disclosed methods, the subject is administered one or more dose of an anti-c-kit antibody or antigen-binding fragment thereof, each of about 0.0073 mg/kg to about 7.3 mg/kg or about 0.01 mg/kg to about 10 mg/kg of the antibody or antigen-binding fragment thereof, optionally about 0.073 mg/kg to about 7.3 mg/kg or 0.1 mg/kg to about 10 mg/kg of the antigen-binding fragment. In certain embodiments, the subject is administered about 0.3 mg/kg, 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.67 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, or about 2 mg/kg of the antibody or antigen-binding fragment thereof.

[0015] In embodiments of any of the methods disclosed herein, the antibody or antigen-binding fragment thereof is delivered to the subject systemically, optionally wherein the antigen-binding fragment is delivered intravenously or subcutaneously. In embodiments of any of the methods disclosed herein, the antibody or antigen-binding fragment thereof is delivered to the subject locally, optionally wherein the antigen-binding fragment is delivered directly to the skin.

[0016] In particular embodiments of the disclosed methods wherein the disease or disorder is a mast cell disease or disorder, the method depletes mast cells, induces mast cell apoptosis, and/or inhibits mast cell degranulation. In certain embodiments, the method depletes mast cells, induces mast cell apoptosis, and/or inhibits mast cell degranulation by at least 50% at about 2 weeks following administration of the antibody or antigen-binding fragment thereof. In certain embodiments, the subject's mast cells are depleted by 20% or less at about 3-4 months following administration of the antibody or antigen-binding fragment thereof.

[0017] In certain embodiments, the disclosure provides pharmaceutical compositions, unit dosage forms, and kits that comprise one or more doses of a monoclonal anti-c-kit IgG antibody

or antigen binding fragment thereof, wherein each of the one or more doses comprises about 40 mg to about 360 mg, about 50 mg to about 600 mg, or about 50 mg to about 300 mg of the anti-c-kit antibody or fragment thereof, optionally wherein the anti-c-kit antibody is JSP191.

[0018] In certain embodiments of any of the methods, compositions, unit dosage forms, or kits disclosed herein, the anti-c-kit antibody or antigen-binding fragment thereof comprises one or more, three or more, four or more, or five or more, optionally six, complementarity-determining regions (CDRs) present in a monoclonal antibody selected from the group consisting of: SR-1, JSP191, MGTA-117, FSI-174, CDX-0159, 8D7, K45, 104D2, CK6, AB249, YB5.B8, AF-2-1, AF11, AF12, AF112, AF-3, AF-1-1, NF, NF-2-1, NF11, NF12, NF112, NF-3, HF11, HF12, and HF112. In certain embodiments, the anti-c-kit antibody comprises one or more, three or more, four or more, or five or more, optionally six, complementarity-determining regions (CDRs) present in a humanized version of a monoclonal antibody selected from the group consisting of: ACK2, ACK4, 2B8, 3C11, MR-1, and CD122, optionally wherein the antibody is an IgG antibody. In certain embodiments, the anti-c-kit antibody or antigen-binding fragment thereof comprises the CDRs of an antibody that blocks the binding of stem cell factor (SCF) to stem cell factor receptor (CD117), optionally wherein the antibody is JSP191 (also called briquilimab) or the antigen-binding fragment thereof is a JSP191 (Fab')₂.

[0019] In certain embodiments of any of the methods, compositions, unit dosage forms, or kits disclosed herein, each dose comprises or consists of about 50 mg to about 600 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 120 mg to about 240 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, or about 600 mg of the anti-c-kit antibody, optionally wherein the antibody is JSP191. In certain embodiments, each dose comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg of the anti-c-kit antibody, optionally wherein the antibody is JSP191. In certain embodiments, the anti-c-kit antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously. In certain embodiments the anti-c-kit antibody is delivered to the subject locally, optionally wherein the anti-c-kit antibody is delivered directly to the skin.

[0020] In another aspect, the disclosure provides a method of altering the differentiation pathway of HSCs and/or HSPCs, comprising contacting the cells with a monoclonal anti-c-kit IgG antibody or antigen-binding fragment thereof, wherein the monoclonal anti-c-kit IgG antibody comprises five or more of the CDRs present in an antibody that inhibits binding of SCF to c-kit on the cell surface. In particular embodiments, the method results in increased differentiation of the cells along the megakaryocytic lineage. In particular embodiments, the anti-c-kit IG antibody is JSP-191 or an antigen-binding fragment thereof, e.g., a F(ab')₂.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 is a diagram of the trial design for the clinical trial described in Example 9.

[0022] FIG. 2 is a diagram of the time course for participants in the clinical trial described in Example 9.

[0023] FIG. 3 is a diagram of the questions and response options with points per response, for determining the UCT score.

[0024] FIG. 4 is a graph showing that briquilimab prevents IgE-Induced PSA in hmCD117 mice. hmCD117 mice were treated with briquilimab, 5 mg/kg, 3 time per week for three weeks or a bolus 25 mg/kg two weeks prior to be sensitized with anti-DNP IgE and challenged 24 hours later with DNP-HSA. Data represent the mean $\pm$ SEM. Statistical analysis was done by comparison of group means from 0 to 60 min. ** $p < 0.01$ by Welch's *t*-test.

[0025] FIG. 5 is a schematic diagram showing how briquilimab may provide protection from severe allergic reactions.

[0026] FIGs. 6A-6C demonstrate that briquilimab prevents IgE-mediated anaphylaxis reactions. FIG. 6A is a diagram of the experimental schema. FIG. 6B provides graphs of core body temperature of animals at the indicated time points after challenge at Weeks 1-4 following briquilimab treatment or untreated. FIG. 6C provides graphs showing the clinical score determined at the indicated time points after challenge at Weeks 1-4 following briquilimab treatment or untreated.

[0027] FIGs. 7A and 7B show mast cell depletion and recovery kinetics following briquilimab in various tissues. FIG. 7A provides mast cells numbers determined at the indicated time point following briquilimab treatment in ear skin, stomach, and tongue. FIG. 7B shows representative images of mast cells from stomach (stained dark purple; indicated by arrows).

[0028] FIG. 8 is a schematic diagram showing how briquilimab may provide protection from severe anaphylactoid reactions.

[0029] FIGs. 9A-9C demonstrate that briquilimab prevents IgE-mediated anaphylaxis reactions. FIG. 9A is a diagram of the experimental schema. FIG. 9B provides graphs of core body temperature of animals at the indicated time points after challenge at Weeks 2-4 following briquilimab treatment or untreated. FIG. 9C provides graphs showing the clinical score determined at the indicated time points after challenge at Weeks 2-4 following briquilimab treatment or untreated.

[0030] FIGs. 10A and 10B show mast cell depletion and recovery kinetics following one-time briquilimab treatment in various tissues. FIG. 10A provides mast cells numbers determined at the indicated time point following briquilimab treatment in ear skin, stomach, and tongue. FIG. 10B shows representative images of mast cells in ear skin (stained dark purple; indicated by arrows).

[0031] FIG. 11 is a graph showing briquilimab serum concentration at the indicated times following administration of the indicated amounts of briquilimab. At each time point, the lower left clump of circles is 5 mg/kg, the middle group of circles is 10 mg/kg, and the right group of circles is 25 mg/ml, which achieves the highest level of briquilimab.

[0032] FIG. 12 provides diagrams of the schema for prophylactic and therapeutic models of asthma tested in h/mCD117 mice.

[0033] FIG. 13 shows briquilimab inhibition of airway inflammation following cockroach allergen sensitization and challenge. The top panel provides representative images of airways from non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals. The bottom panel provides graphs showing amounts of BALF neutrophils, airway-infiltrated neutrophils, and airway-infiltrated eosinophils in non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals.

[0034] FIG. 14 shows reduction of mast cells following treatment with briquilimab. The upper panel provides representative images of lung mast cells (Lung MCs) and back skin mast cells (Back Skin MCs) from non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals, with darkly stained mast cells indicated by arrows. The lower panel provides graphs showing amounts of lung and back skin mast cells in non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals.

[0035] FIG. 15 shows briquilimab prevention of recurrence of asthma exacerbation following allergen exposure. The panels provide representative images of airways from non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals, and graphs summarizing the amount of BALF PMNs and airway PMNs present. The line graph provides a graph showing pulmonary resistance following treatment with the indicated amount of

methacholine in non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals. At 40 mg/ml methacholine, the lines from top to bottom correspond to asthma, asthma+Briq, and non-asthma (PBS).

[0036] FIG. 16 shows briquilimab decreases mast cells following allergen exposure. The upper panel provides representative images of lung and back skin tissue showing mast cells (MCs) present in non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals. Darkly stained mast cells are indicated with arrows. The lower panel provides graphs showing amounts of lung and back skin mast cells in non-asthma (PBS), asthma, and asthma treated with briquilimab (asthma+Briq) animals.

[0037] FIGs. 17A-17L show briquilimab depletes MCs in various tissues of NHP. (FIG. 17A) After a single SC (0.1, 1, 10 mg/kg) administration of briquilimab to sexually mature male African green monkeys, non-linear PK was observed in the mean serum concentration-time profiles and (FIG. 17B) the mean PK parameter values. The C_{max} increased 25-fold from 0.1 to 1 mg/kg dosing and 9.7-fold from 1 to 10 mg/kg dosing, respectively. The AUC_{last} increased 78- and 17-fold for 10-fold increases in dose from 0.1 to 1 mg/kg and 1 to 10 mg/kg, respectively. (FIG. 17C) c-Kit⁺ MC number in the colon submucosa was significantly decreased 49 days after a single dose of 1 or 10 mg/kg of briquilimab. The MC number in the 0.1 mg/kg dose group was also lower than controls although not statistically significant. (FIG. 17D) MC quantification using tryptase⁺ as a marker showed the similar pattern of MC decrease by briquilimab in a dose-dependent manner. (FIG. 17E) After skin incisional wounding, the adjacent skin MC number decreased initially irrespective of briquilimab treatment reaching a nadir at 3-7 days post-wounding. In the absence of briquilimab, the MC number increased subsequently, while a single briquilimab dose at 10 mg/kg maintained the MC number low throughout the study period. At briquilimab doses lower than 10 mg/kg, the skin MC suppression was more modest and MC number rebounded as the wound healed although less than the control group. (FIG. 17F) A repeat-dose (0 (vehicle/placebo), 0.3, 1, or 3 mg/kg) pharmacology study of briquilimab administered once weekly for 4 weeks to African Green monkeys resulted in decreased numbers of submucosal MCs in colon in a dose-dependent manner with 50 to 99% depletion compared to baseline on day 28. (FIGs. 17G and 17H) The effect of briquilimab treatment was also evaluated in the wounded skin biopsies on days 0, 4, 7, 14, 21. While the skin incisional wounding resulted in increased dermal MCs adjacent to the wound in the placebo control group over time, this increase was prevented by all three doses of briquilimab tested as shown by % of c-Kit⁺ and (FIG. 17H) tryptase⁺ MCs at each time point compared to Day 0. (FIGs. 17I-17L) Resident interstitial (within alveolar walls; FIGs. 17I and

17J) and peribronchiolar (near the hilus; FIGs. 17K and 17L) lung MCs were depleted to 5 to 50% of placebo control in a dose-dependent manner at day 28. The extent of depletion varied among the MC markers used and the morphologic locations of lung.

[0038] FIGs. 18A-18C show that briquilimab is generally well-tolerated in NHPs. (FIG. 18A) Administration of briquilimab once weekly by SC injection to cynomolgus monkeys for 1 month at 1, 10, and 300 mg/kg/dose was well-tolerated in both sexes (female data shown). Briquilimab at all doses resulted in a transient decrease in absolute reticulocyte count at day 15 of the dosing phase (FIG. 18B) A mild to moderate decrease (6 to 10% decrease from predose levels for 1 mg/kg/dose and 14 to 19% for 10 and 300 mg/kg/doses, respectively) in red cell mass (hemoglobin level is shown as a representative data) and (FIG. 18C) the white blood cell (neutrophil data is shown) counts were also maintained within the hematological reference range of cynomolgus monkeys (Koo et al.)

[0039] FIGs. 19A-19E show that briquilimab exhibits a dose-dependent mast cell depletion in healthy volunteers and predictable pharmacokinetics. FIG. 19A is a graph showing maximum serum concentrations of briquilimab were typically observed within one week of dosing and the overall serum concentration-time profile was suggestive of nonlinear pharmacokinetics attributable to target mediated drug disposition. Briquilimab serum exposures increased more than dose proportionally in the 0.7 mg to 280 mg dose range evaluated with nearly dose proportional increase at the highest dose levels of 158 mg and 280 mg. FIG. 19B and FIG. 19C show briquilimab serum C_{max} and AUC_{last} values (data shown for ≥ 42 mg dose levels) were comparable in female and male participants indicating no difference in pharmacokinetics FIG. 19D shows briquilimab dose related impairment of MC recovery as evidenced by substantially lower c-Kit-positive skin MCs on Day 29 at ≥ 84 mg dose levels when compared to placebo and lower dose levels (data from only 42 mg dose level shown). When compared to baseline, on Day 29, mean percent increase in c-Kit-positive skin MCs was 121% and 64% after placebo and 42 mg briquilimab, respectively, and mean percent decrease in c-Kit-positive skin MCs was 58%, 75% and 84% after 84 mg, 158 mg and 280 mg briquilimab, respectively. FIG. 19E shows depletion of CD117-positive (left panel) and tryptase-positive (right panel) mast cells (MC) following the indicated briquilimab treatments over 29 days. At day 29, the lines from top to bottom in the left panel correlate with: placebo; 10 mg SC; 20 mg SC; 42 mg SC; 0.5 mg IV; 84 mg SC; 158 mg SC; and 280 mg SC. At day 29, the lines from top to bottom in the right panel correlate with: 0.5 mg IV; 10 mg SC; 20 mg SC; placebo; 42 mg SC; 84 mg SC; 158 mg SC; and 280 mg SC.

[0040] FIGs. 20A-20C show that briquilimab leads to transient decreases in white blood cells, neutrophils and hemoglobin in healthy volunteers. Mean values for white blood cells (FIG. 20A), neutrophils (FIG. 20B), and hemoglobin (FIG. 20C) are shown for briquilimab $\geq$ 42 mg dose levels, and the shaded area represents range of values observed in participants receiving placebo. Decreases in laboratory values were transient, reversible and were not accompanied by clinical signs or symptoms.

[0041] FIGs. 21A-21K show briquilimab inhibition of SCF/c-Kit signaling, MC degranulation, and survival more potently than JSP084 and imatinib. FIG. 21A shows antibody binding to c-Kit; FIG. 21B shows blocking of SCF binding to c-Kit; FIG. 21C shows inhibition of SCF-mediated c-Kit receptor internalization; and FIG. 21D shows c-Kit phosphorylation by briquilimab, JSP084, and imatinib in M-07e cells. FIG. 21E shows the level of c-Kit phosphorylation in M-07e cells, and FIG. 21F shows Akt phosphorylation in Ba/F3 cell line stably transduced to overexpress human c-Kit and their inhibition by briquilimab and JSP084. Inhibition of M-07e cell proliferation (FIG. 21G), survival of primary MC differentiated from human CD34 cells (FIG. 21H), and IgE-dependent MC degranulation by briquilimab, JSP084, and imatinib (FIG. 21I) are also shown. Aglycosylated briquilimab via N297Q mutation did not induce Fc γ R-mediated degranulation of primary MC cells in response to IFN γ (FIG. 21J) nor ADCC (FIG. 21K) on M-07e target cells.

[0042] FIGs. 22A-22D show briquilimab binding to c-Kit (FIG. 22A), blocking SCF binding to c-Kit (FIG. 22B), SCF mediated c-Kit internalization (FIG. 22C), and c-Kit phosphorylation in M-07e cells (FIG. 22D).

[0043] FIGs. 23A-23B show that briquilimab does not induce apoptosis of healthy HSC. FIG. 23A shows total live cells following the indicated treatments, and FIG. 23B shows the number of live cells and apoptotic cells following the indicated treatments.

[0044] FIGs. 24A-24D show that briquilimab skews HSC differentiation into an alternative pathway. FIG. 24A shows flow cytometry plots of CD34 and CD38 expression and fold change of Mean Fluorescence Intensity (MFI) of CD34 and CD38 expression on the cell surface following the indicated treatments at indicated timepoints. FIG. 24B shows the HSC and each progenitor cell number as defined based on cell markers at the indicated time points following the indicated treatments. Multipotent progenitor: MPP (CD34+CD38-CD90-CD45RA-), Common myeloid progenitor: CMP (CD34+CD38+CD45RA-CD123^{low}), Granulocyte-monocyte progenitor: GMP(CD34+CD38+CD45RA+ CD123^{low}), Megakaryocyte-erythrocyte progenitor: MEP(CD34+CD38+CD45RA-CD123-). FIG. 24C is a diagram of the classical scheme of HSC differentiation into the myeloid lineage and expression pattern of

CD34 and CD38 on HSC and progenitor cells. FIG. 24D provides a flow cytometry plot of c-Kit expression in each group and a graph showing the fold change of c-Kit expression on the cell surface at the indicated timepoints following the indicated treatments.

[0045] FIG. 25 provides a hypothetical working model of how the blocking of SCF/c-Kit signaling by briquilimab skews HSC towards a distinct alternative HSC differentiation pathway in ex vivo culture.

[0046] FIGs. 26A and 26B compare the pharmacokinetic profiles of briquilimab (JSP191) and barzolvolimab (CDX-0159) in humans following intravenous injection. The serum concentration of briquilimab following intravenous (IV) injections in patients in a clinical trial for severe combined immunodeficiency (SCID) were plotted against the drug doses (FIG. 26A). A reported PK chart for barzolvolimab (CDX-0159) following intravenous (IV) injection in healthy volunteers is included as FIG. 26B for comparison. In FIG. 26B, the lines from top to bottom at 21 days correspond to the doses indicated in the legend from top to bottom.

[0047] FIGs. 27A and 27B compare the pharmacokinetic profiles of briquilimab (FIG. 27A) and barzolvolimab (FIG. 27B) in humans following subcutaneous (SC) injection.

[0048] FIG. 28 is a diagram of the trial design for the clinical trial described in Example 10.

DETAILED DESCRIPTION OF THE INVENTION

[0049] The present disclosure provides *inter alia* treatments for mast cell-related diseases and disorders using anti-c-kit antibodies and fragments thereof in a dose effective to deplete mast cells in a subject being treated. In certain embodiments, the methods are used to treat chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), prurigo nodularis, eosinophilic esophagitis, allergic asthma and severe, asthma, inflammatory bowel disease, and other mast cell-related diseases and disorders, including, but not limited to, those disclosed herein.

[0050] In particular embodiments, the disclosure provides agents and dosing regimens effective in depleting mast cells while not adversely depleting healthy hematopoietic stem cells in treated patients, and related methods of treating mast cell-related diseases and disorders. In particular embodiments, the methods are practiced using the anti-c-Kit antibody, JSP191 or briquilimab, a humanized, aglycosylated IgG1 inhibitor of c-Kit signaling on mast cells, which directly blocks stem cell factor (SCF) binding to CD117. Briquilimab's sequence/structure and mechanism of action provide it with a potency and a half-life that is advantageous for depleting mast cells without substantially depleting healthy hematopoietic stem cells, thus making briquilimab superior for treating, preventing, or inhibiting mast cell-related diseases and

disorders. The disclosure further provides dosing regimens that facilitate treatment, prevention, and inhibition of various types of mast cell-related diseases and disorders, including but not limited to single high dose regimens and repeat dosing regimens with intervals between doses.

[0051] The present disclosure also provides treatments for hematopoietic stem/progenitor cell diseases and disorders using anti-c-kit antibodies and fragments thereof.

Definitions

[0052] It is to be understood that this invention is not limited to the particular methodology, products, apparatus and factors described, as such methods, apparatus and formulations may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and it is not intended to limit the scope of the present invention which will be limited only by appended claims.

[0053] It must be noted that as used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a drug candidate" refers to one or mixtures of such candidates, reference to "the method" includes reference to equivalent steps and methods known to those skilled in the art and so forth, and, for example, "an antibody," is understood to represent one or more antibodies. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

[0054] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

[0055] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention. The disclosure also contemplates ranges having upper and lower limits defined by any two numerical values disclosed separately herein.

[0056] As used herein, "antibody" includes reference to an immunoglobulin molecule immunologically reactive with a particular antigen, and includes both polyclonal and monoclonal antibodies. In certain embodiments, an antibody comprises two heavy chains and two light chains, wherein each light chain is bound to a different heavy chain, and the two heavy chains are bound to each other. Five types of immunoglobulins include IgM, IgG, IgA, IgE, and IgD2. Antibodies may be any of these, and in certain embodiments are IgG. The term also includes genetically engineered forms such as humanized antibodies, chimeric antibodies (*e.g.*, humanized murine antibodies) and heteroconjugate antibodies. An antibody can be a whole antibody and any antigen binding fragment or a single chain thereof. Thus, the term "antibody" includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule having biological activity of binding to the antigen. Examples of such include, but are not limited to a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region, or any portion thereof, or at least one portion of a binding protein. The term "antibody" also includes antigen-binding forms of antibodies, including fragments with antigen-binding capability (*e.g.*, Fab', F(ab')₂, Fab, Fv and rIgG. The term also refers to recombinant single chain Fv fragments (scFv). The term antibody also includes bivalent or bispecific molecules, diabodies, triabodies, and tetrabodies.

[0057] The terms "antibody fragment" or "antigen-binding fragment", as used herein, is a portion of an antibody such as F(ab')₂, F(ab)₂, Fab', Fab, Fv, scFv, and the like. Regardless of structure, an antibody fragment binds to the same antigen that is recognized by the intact antibody. The term "antibody fragment" includes aptamers, spiegelmers, and diabodies. The term "antibody fragment" also includes any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex.

[0058] A "humanized antibody" is an immunoglobulin molecule which contains minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond

to those of a non-human immunoglobulin and all or substantially all of the framework (FR) regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin.

[0059] Selection of antibodies for cell ablation, e.g., ablation of endogenous mast cells, may be based on a variety of criteria, including selectivity, affinity, cytotoxicity, etc. By "specifically binds" or "has specificity to," it is generally meant that an antibody binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity between the antigen-binding domain and the epitope. According to this definition, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen-binding domain more readily than it would bind to a random, unrelated epitope. Thus, the phrase "specifically (or selectively) binds", when referring to an antibody binding to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein, in a heterogeneous population of proteins and/or other biologics. The term "specificity" is used herein to qualify the relative affinity by which a certain antibody binds to a certain epitope. For example, antibody "A" may be deemed to have a higher specificity for a given epitope than antibody "B," or antibody "A" may be said to bind to epitope "C" with a higher specificity than it has for related epitope "D." Thus, in some embodiments, under designated immunoassay conditions, the specified antibodies bind to a particular protein sequence at least two times the background binding and more typically more than 10 to 100 times background binding.

[0060] Monoclonal antibodies may be prepared using hybridoma methods. In a hybridoma method, an appropriate host animal is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized in vitro. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell.

[0061] Human antibodies can be produced using various techniques known in the art, including phage display libraries. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire.

[0062] Antibodies also exist as a number of well-characterized fragments produced by digestion with various peptidases. Pepsin digests an antibody below the disulfide linkages in the hinge region to produce F(ab')₂, a dimer of Fab which itself is a light chain joined to VH-CH1 by a disulfide bond. The F(ab')₂ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the F(ab')₂ dimer into a Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region. While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized de novo either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized de novo using recombinant DNA methodologies (*e.g.*, single chain Fv) or those identified using phage display libraries.

[0063] The selectivity of a particular antibody is typically determined by the ability of one antibody to competitively inhibit binding of the second antibody to the antigen, or by the ability of an antibody to cross-react with multiple epitopes. Any of a number of competitive binding assays can be used to measure competition between two antibodies to the same antigen, or between two antigens to one antibody. An exemplary assay is a BIACORE™ assay. Briefly in these assays, binding sites can be mapped in structural terms by testing the ability of interactants, *e.g.*, different antibodies, to inhibit the binding of another. Injecting two consecutive antibody or antigen samples in sufficient concentration can identify pairs of competing antibodies for the same binding epitope. The antibody samples should have the potential to reach a significant saturation with each injection. The net binding of the second antibody injection is indicative for binding epitope analysis. Two response levels can be used to describe the boundaries of perfect competition versus non-competing binding due to distinct epitopes. The relative amount of binding response of the second antibody injection relative to the binding of identical and distinct binding epitopes determines the degree of epitope overlap.

[0064] The term "polynucleotide" refers to a polymeric form of nucleotides of any length, including deoxyribonucleotides or ribonucleotides, or analogs or mixtures thereof. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide or nucleoside analogs, and may be interrupted by non-nucleotide components. In the present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The term polynucleotide, as used herein, includes, but is not limited to, double- and single-stranded molecules, and mixtures thereof. Unless otherwise specified or required, any embodiment of the invention described herein that is a polynucleotide encompasses both

the double-stranded form and each of two complementary single-stranded forms known or predicted to make up the double-stranded form, whether as RNA or DNA, or a mixture thereof.

[0065] "Encoding" refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (*i.e.*, rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0066] As used herein, the terms "polypeptide," "peptide," and "protein" refer to polymers of amino acids of any length. The terms also encompass an amino acid polymer that has been modified; for example, to include disulfide bond formation, glycosylation, lipidation, phosphorylation, or conjugation with a labeling component. The term "polypeptide" is intended to encompass a singular "polypeptide" as well as plural "polypeptides," and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term "polypeptide" refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, peptides, dipeptides, tripeptides, oligopeptides, "protein," "amino acid chain," or any other term used to refer to a chain or chains of two or more amino acids, are included within the definition of "polypeptide," and the term "polypeptide" may be used instead of, or interchangeably with any of these terms. The term "polypeptide" is also intended to refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non-naturally occurring amino acids. A polypeptide may be derived from a natural biological source or produced by recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It may be generated in any manner, including by chemical synthesis.

[0067] As used herein, the terms "identity" and "identical" refer, with respect to a polypeptide or polynucleotide sequence-of-interest, to the percentage of exact matching residues in an alignment of that the sequence-of-interest to a reference sequence, such as an alignment generated by the BLAST algorithm. Identity is calculated, unless specified otherwise, across

the full length of the reference sequence. Thus a sequence-of-interest “shares at least x% identity to” a reference sequence if, when the reference sequence is aligned (as a query sequence) is aligned to the sequence-of-interest (as subject sequence), at least x% (rounded down) of the residues in the subject sequence are aligned as an exact match to a corresponding residue in the query sequence, the denominator being the full length of the reference sequence plus the lengths of any gaps inserted into the reference sequence by alignment of the reference sequence to the sequence-of-interest. Where the subject sequence has variable positions (*e.g.*, residues denoted X), an alignment to any residue in the query sequence is counted as a match. Sequence similarity (*i.e.*, identity) can be determined in a number of different manners. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the worldwide web at ncbi.nlm.nih.gov/BLAST/. Sequence alignments may be performed using the NCBI Blast service (BLAST+ version 2.12.0) or another program giving the same results. Unless indicated to the contrary, sequence identity is determined using the BLAST algorithm (*e.g.*, bl2seq) with default parameters.

[0068] The term "native" or “wild-type” as used herein refers to a nucleotide sequence, *e.g.*, gene, or gene product, *e.g.*, RNA or polypeptide, that is present in a wild-type cell, tissue, organ or organism. The term “variant” as used herein refers to a mutant of a reference polynucleotide or polypeptide sequence, for example a native polynucleotide or polypeptide sequence, *i.e.*, having less than 100% sequence identity with the reference polynucleotide or polypeptide sequence. Put another way, a variant comprises at least one amino acid difference (*e.g.*, amino acid substitution, amino acid insertion, amino acid deletion) relative to a reference polynucleotide sequence, *e.g.*, a native polynucleotide or polypeptide sequence. For example, a variant may be a polynucleotide having a sequence identity of 50% or more, 60% or more, or 70% or more with a full length native polynucleotide sequence, *e.g.*, an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the full length native polynucleotide sequence. As another example, a variant may be a polypeptide having a sequence identity of 70% or more with a full length native polypeptide sequence, *e.g.*, an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the full length native polypeptide sequence. Variants may also include variant fragments of a reference, *e.g.*, native, sequence sharing a sequence identity of 70% or more with a fragment of the reference, *e.g.*, native, sequence, *e.g.*, an identity of 75% or 80% or more, such as 85%, 90%, or 95% or more, for example, 98% or 99% identity with the native sequence.

[0069] The term “stem cell” as used herein refers to a mammalian cell that has the ability both to self-renew, and to generate differentiated progeny (see Morrison et al. (1997) Cell 88:287-298). Endogenous stem cells may be characterized by the presence of markers associated with specific epitopes. The term “hematopoietic stem cells (HSC)” as used herein refers to multipotent cells that reside in the bone marrow (BM) and are responsible for the life-long production of mature blood cells. HSCs have the capacity to give rise to all the different types of mature blood cells, including red blood cells (erythrocytes), white blood cells (leukocytes), and platelets.

[0070] “Hematopoietic stem and progenitor cells” (HSPCs) are a group of cells that are responsible for the generation and replenishment of all the different types of blood cells in the body. They are located primarily in the bone marrow, although small populations can also be found in peripheral blood and umbilical cord blood. HSCs are the most primitive and self-renewing cells within the HSPC population. They possess the ability to both replicate themselves through self-renewal and differentiate into multiple specialized cell types. HSPCs also include progenitor cells, which are more committed and lineage-restricted than HSCs. Progenitor cells arise from HSCs and undergo a limited number of cell divisions before differentiating into specific blood cell lineages. Progenitor cells are considered to be more differentiated than HSCs but less differentiated than fully mature blood cells.

[0071] The terms “treatment”, “treating” and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. “Treatment” as used herein covers any treatment of a disease in a mammal, and includes, e.g.: (a) inhibiting the progression of a disease, i.e., arresting or delaying its development; (b) reducing the severity of the disease; or (c) relieving the disease, i.e., causing regression of the disease. “Treatment” is an intervention performed with the intention of preventing the progression of, or altering the pathology of, a disease or disorder. Accordingly, “treat” or “treatment” refers to therapeutic treatment, whereas “prevent” or “prevention” refers to prophylactic or preventative measures, including delaying the onset of a disease or disorder or recurrence of a disease or disorder. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. In particular embodiments, treatment results in improvement in one or more symptoms of the disease. To “inhibit” or “prevent” a disease or disorder includes delaying the onset or reducing the severity of a disease or disorder, or causing the disease or disorder to not occur, e.g., an allergic reaction.

[0072] As used herein, the phrase “therapeutically effective amount,” in the context of treating a mast cell-related disease or disorder, is meant to refer to an amount of therapeutic or prophylactic anti-CD117 antibody that provides a reduction in mast cell number and/or activity, reduction in fibroid elements or their precursors, or that provides a reduction in the severity or progression of symptoms associated with a mast cell-related disease (i.e., that provides “therapeutic efficacy”).

[0073] The terms "individual," "host," "subject," and "patient" are used interchangeably herein, and refer to a mammal, including, but not limited to, human and non-human primates, including simians and humans; mammalian sport animals (e.g., horses); mammalian farm animals (e.g., sheep, goats, etc.); mammalian pets (dogs, cats, etc.); and rodents (e.g., mice, rats, etc.).

[0074] As used herein, the term “substantially” means by a significant or large amount or degree. For example, to “substantially” increase may mean to increase by at least two-fold, at least three-fold, at least four-fold, at least five-fold, or at least ten-fold, and to “substantially” decrease may mean to decrease by at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%. In the following description, numerous specific details are set forth to provide a more thorough understanding of the present invention. However, it will be apparent to one of skill in the art that the present invention may be practiced without one or more of these specific details. In other instances, well-known features and procedures well known to those skilled in the art have not been described in order to avoid obscuring the invention.

[0075] Generally, conventional methods of protein synthesis, recombinant cell culture and protein isolation, and recombinant DNA techniques within the skill of the art are employed in the present invention. Such techniques are explained fully in the literature, see, e.g., Maniatis, Fritsch & Sambrook, *Molecular Cloning: A Laboratory Manual* (1982); Sambrook, Russell and Sambrook, *Molecular Cloning: A Laboratory Manual* (2001); Harlow, Lane and Harlow, *Using Antibodies: A Laboratory Manual: Portable Protocol No. I*, Cold Spring Harbor Laboratory (1998); and Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory; (1988).

Treatment of Mast Cell-Related Diseases and Disorders

[0076] The tyrosine-protein kinase KIT is also known as c-KIT, CD117 (cluster of differentiation 117) or SCFR (mast/stem cell growth factor receptor). C-KIT is expressed on the surface of hematopoietic stem cells, mast cells, neural crest-derived melanocytes, and germ cells. C-KIT binds to stem cell factor (SCP) and forms a dimer that activates its intrinsic

tyrosine kinase activity, which in turn phosphorylates and activates signal transduction molecules that propagate the signal in the cell.

[0077] The human c-KIT protein has an extracellular domain (ECD) with 5 Ig-like domains (D1-D5), which are implicated in ligand binding and homodimerization, a transmembrane domain, and an intracellular domain (ICD). Protein processing of c-KIT includes N-linked glycosylation and phosphorylation on both tyrosine and serine residues. When SCP dimers bind to c-KIT, the binding induces c-KIT dimerization, conformational change of both ECD and ICD, ICD trans-phosphorylation and binding of various partners.

[0078] Mast cells are a key cellular target for a variety of inflammatory and immune diseases, including autoimmune diseases. CD117 is important for the development and differentiation of mast cells from hematopoietic stem cells in the bone marrow. The binding of stem cell factor (SCF) to CD117 initiates signaling cascades that promote mast cell growth and maturation. CD117 signaling through SCF is crucial for the survival and proliferation of mast cells. SCF binding to CD117 activates various intracellular signaling pathways, including the PI3K-AKT and MAPK pathways, which regulate cell survival and cell cycle progression. CD117 is also involved in mast cell migration and homing to various tissues. Mast cells express CD117 on their surface, allowing them to respond to SCF gradients and migrate to specific locations where SCF is present, such as the skin, respiratory tract, and gastrointestinal tract. CD117 signaling contributes to mast cell activation and degranulation. When mast cells encounter allergens or antigens, cross-linking of IgE antibodies bound to FcεRI receptors on the mast cell surface triggers a signaling cascade that involves CD117. This signaling enhances the release of various inflammatory mediators, such as histamine, cytokines, chemokines, and proteases, which are responsible for allergic reactions and immune responses. CD117 signaling influences multiple aspects of mast cell function. It modulates the expression of cell surface receptors, such as FcεRI and other immune receptors, and regulates the production and release of various cytokines and chemokines by mast cells. These processes contribute to the immune response and the recruitment of other immune cells to the site of inflammation.

[0079] Inhibition of c-Kit signaling can lead to organized cell death and phagocytic clearance of mast cells. On the one hand, however, the blockade needs to be higher than a threshold level to deplete the mast cells, as partial c-Kit inhibition can only inhibit mast cell activation. On the other hand, sustained c-Kit blockade can result in undesirable effects on other c-Kit-expressing cells. Such a tension, therefore, presents a significant challenge for developing c-Kit antibodies for treating mast cell-mediated diseases and disorders.

[0080] Briquilimab (JSP191) is an anti-c-Kit antibody under clinical development. A benchmark anti-c-Kit antibody is barzolvolimab (CDX-0159) being developed by Celldex Therapeutics Inc. In an unexpected discovery, briquilimab exhibited more rapid pharmacokinetic clearance as compared to barzolvolimab. The shortened drug exposure, however, was still sufficient for mast cell depletion, which occurs rather quickly as well. Such improved clearance, therefore, presents a unique advantage for briquilimab, as it can help minimize adverse effects on other, non-targeted, c-Kit-positive cells.

[0081] Yet another advantage of briquilimab is that it can be more potent than barzolvolimab, at least at lower doses. While the clinical dose of barzolvolimab for treating chronic urticaria is 3 mg/kg (Terhorst-Malawi *et al.*, *Allergy*. 2023;78:1269-1279), briquilimab exhibited potent and lasting efficacy at doses as low as about 1 mg/kg.

[0082] Activation of the c-Kit upon binding by stem cell factor (SCP) leads to dimerization, autophosphorylation and receptor internalization. The conventional antibody barzolvolimab inhibits c-Kit activity by inhibiting c-Kit dimerization. It has been shown, however, briquilimab blocks the interaction between c-Kit and SCP directly, whose receptor antagonism is accordingly likely more potent.

[0083] In accordance with certain embodiments of the present disclosure, provided is a method for treating a mast cell-related or mast cell-mediated disease or disorder in a subject in need thereof, comprising administering to the subject an effective amount of an anti-CD117 antibody or an antigen binding fragment thereof. Illustrative antibodies and antigen-binding fragments thereof include, but are not limited to, those disclosed herein. In certain embodiments, the anti-CD117 antibody comprises a heavy chain variable region comprising the amino acid sequence of the heavy chain variable region of JSP191 and a light chain variable region comprising the amino acid sequence of the light chain variable region of JSP191. In certain embodiment, the antibody is JSP191 or an antigen binding fragment thereof.

[0084] The disclosure contemplates the treatment or prevention of any mast cell-related or mast cell-mediated disease or disorder, and these terms are used interchangeably herein. In some embodiments, the mast cell-mediated disease or disorder is selected from the group consisting of urticaria, asthma, prurigo nodularis (PN), eosinophilic esophagitis (EoE), mastocytosis, urticaria pigmentosa, anaphylaxis, endometriosis, interstitial cystitis, and mast cell activation syndrome (MCAS). In particular embodiments, the mast cell-related disease or disorder is selected from the group consisting of: urticarias, optionally chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), chronic idiopathic urticaria (CIU), or urticaria pigmentosa, prurigo nodularis, esophagitis, optionally eosinophilic esophagitis,

asthma, allergic diseases and disorders, optionally allergic asthma, anaphylaxis, mastocytosis, mast cell activation syndrome (MCAS), fibrosis, dermatitis, atherosclerosis, endometriosis, interstitial cystitis and inflammatory bowel disease.

[0085] In some embodiments, the mast cell-mediated disease or disorder is a urticaria, e.g., a chronic urticaria. In some embodiments, the chronic urticaria is chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIndU). In some embodiments, the CIndU is Cold urticaria (ColdU) or Symptomatic Dermographism (SD).

[0086] In some embodiments, the methods and treatments described herein deplete mast cells from a subject by administering an anti-c-kit antibody or fragment thereof to the subject (e.g., briquilimab or a JSP191 (Fab')₂). In some embodiments, the mast cells comprise activated mast cells. In some embodiments, the mast cells are depleted from one or more tissues or organs of the subject, e.g., in certain embodiments, mast cells are depleted from the skin or lung of the subject. In some embodiments, mast cells are depleted from the subject, or a tissue or organ of the subject, by at least or about 2%, at least or about 5%, at least or about 10%, at least or about 20%, at least or about 30%, at least or about 40%, at least or about 50%, at least or about 60%, at least or about 70%, at least or about 80%, at least or about 90%, at least or about 95%, at least or about 98%, at least or about 99%, or about 100% of total mast cells in the subject, or the tissue or organ of the subject. In certain embodiments, the treatments completely or almost completely deplete mast cells from the subject, or one or more tissue or organ of the subject. In certain embodiments, the tissue or organ is skin or lung.

[0087] In some embodiments, the methods and treatments described herein induce apoptosis of mast cells in a subject by administering an anti-c-kit antibody (e.g., briquilimab) or antigen-binding fragment thereof to the subject. In some embodiments, the mast cells comprise activated mast cells. In some embodiments, the methods induce apoptosis of mast cells in one or more tissues or organs of the subject, e.g., in certain embodiments, in the skin or lung of the subject. In some embodiments, the methods induce apoptosis of mast cells in the subject, or in a tissue or organ of the subject, by at least or about 2%, at least or about 5%, at least or about 10%, at least or about 20%, at least or about 30%, at least or about 40%, at least or about 50%, at least or about 60%, at least or about 70%, at least or about 80%, at least or about 90%, at least or about 95%, at least or about 98%, at least or about 99%, or at least or about 100% of total mast cells in the subject, or the tissue or organ of the subject. In certain embodiments, the treatments induce apoptosis of completely or almost completely all mast cells in the subject, or one or more tissue or organ of the subject. In certain embodiments, the tissue or organ is skin or lung.

[0088] In some embodiments, the treatments described herein selectively deplete or induce apoptosis of activated mast cells in a subject. In particular embodiments, selective depletion or apoptosis of activated mast cells according to a disclosed method results in the depletion or apoptosis of a greater number or percentage of activated mast cells as compared to the number or percentage of non-activated mast cells that are depleted or undergo apoptosis.

[0089] In certain embodiments, methods disclosed herein are used to modulate one or more mast cell activities, e.g., to inhibit mast cell growth and maturation, inhibit mast cell survival and proliferation, inhibit activation of mast cell intracellular signaling pathways, including the PI3K-AKT and MAPK pathways, inhibit mast cell migration and homing to various tissues, e.g., skin, respiratory tract, and gastrointestinal tract tissues, inhibit mast cell activation and degranulation, and/or inhibit mast cell release of various inflammatory mediators, such as histamine, cytokines, chemokines, and proteases.

[0090] In some embodiments, the methods described herein deplete mast cells from a subject by administering an anti-c-kit antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂ fragment, to the subject. In some embodiments, the mast cells comprise activated mast cells. In some embodiments, the mast cells are depleted from one or more tissues or organs of the subject, e.g., in certain embodiments, mast cells are depleted from the skin or lung of the subject. In some embodiments, mast cells are depleted from the subject, or a tissue or organ of the subject, by at least or about 2%, at least or about 5%, at least or about 10%, at least or about 20%, at least or about 30%, at least or about 40%, at least or about 50%, at least or about 60%, at least or about 70%, at least or about 80%, at least or about 90%, at least or about 95%, at least or about 98%, at least or about 99%, or at least or about 100% of total mast cells in the subject, or the tissue or organ of the subject. In certain embodiments, the treatments completely or almost completely deplete mast cells from the subject, or one or more tissue or organ of the subject. In certain embodiments, the tissue or organ is skin or lung.

[0091] In particular embodiments, the methods deplete mast cells, induce mast cell apoptosis, and/or inhibit mast cell degranulation. In certain embodiments, the methods deplete at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or all of the subject's mast cells, or induces apoptosis of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or all of the subject's mast cells, at about one week, two weeks, three weeks, or one month following administration of the antibody. In certain embodiments, the subject's mast cells are depleted by about 5% or less, about 10% or less, or

about 20% or less at about three months, about four months, about five months, about six months, about seven months, about eight months, about nine months, about ten months, about 11 months, or about 12 months following administration of the antibody. In particular embodiments, the depleted mast cells comprise or are activated mast cells.

[0092] In some embodiments, the treatments described herein selectively deplete activated mast cells in a subject. In particular embodiments, selective depletion of activated mast cells according to a disclosed method results in the depletion of a greater number or percentage of activated mast cells as compared to the number or percentage of non-activated mast cells that are depleted.

[0093] In some embodiments, the methods and treatments described herein selectively deplete mast cells as opposed to hematopoietic stem and progenitor cells (HSPCs). In particular embodiments, the methods result in depletion of less than about 10%, less than about 20%, less than about 30%, less than about 40%, or less than about 50% of the subject's HSPCs at about one week, two weeks, three weeks, or one month following administration of the antibody. In particular embodiments, the methods result in depletion of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the subject's activated mast cells or total mast cells. In particular embodiments, HSPCs refer to those measured in the subject's bone marrow, blood or serum. In particular embodiments, mast cells (activated or not) refer to those measured in the subject's bone marrow, blood or serum, or in a tissue sample of the subject, e.g., a skin biopsy.

[0094] Without wishing to be bound to any particular theory, the anti-c-Kit antibodies disclosed herein are shown to induce apoptosis of mast cells. In particular embodiments, they may be used to treat mast cell diseases and disorders. For example, the disclosure contemplates that an anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered to a subject having a mast cell-related disease or disorder at a dosage sufficient to cause mast cell depletion. The mast cells undergo apoptosis, which occurs within hours to days following administration of the anti-c-Kit antibody or fragment thereof. The mast cells are then phagocytized with depletion occurring as early as day 7 with robust depletion at day 29 (about two weeks or more to leave the skin), after which it typically takes mast cells about three months or longer to recover in the skin. JSP191 has a PK clearance half life of about nine days. Following a dose free interval, e.g., anywhere between about eight weeks to about six months, e.g., about eight weeks to about 12 weeks, which allows for return of c-Kit signaling in other c-Kit expressing cells, the subject may be re-dosed with the anti-c-Kit antibody or fragment thereof, e.g., JSP191, or fragment thereof, which causes the apoptosis and phagocytosis of any newly formed

mast cells or mast cell progenitors. This cycle of re-dosing may be continued in order to keep mast cell levels low. Alternatively, a single dose may be sufficient to deplete mast cells associated with a mast cell-related disease or disorder, and there may be no need for re-dosing to remove newly formed mast cells, which may be healthy and/or not activated or not associated with a disease or disorder. In certain embodiments, the methods offer the advantage of long term depletion of mast cells associated with a disease or disorder, while still allowing other cells to resume c-Kit signaling once the anti-c-Kit antibody is cleared.

[0095] In particular embodiments, the anti-c-kit antibody or fragment thereof is provided to the subject in a dose effective to deplete mast cells in a subject being treated.

[0096] In particular embodiments, the subject is provided two or more doses of the anti-c-Kit antibody or fragment thereof, e.g., JSP191, each dose about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In some embodiments, the anti-CD117 antibody or fragment thereof is administered at a dose of 0.8 mg/kg to 5 mg/kg. In some embodiments, the administration is about once every 2-12 weeks or once every 8 weeks to six months. In some embodiments, the administration is once every 4-8 weeks, once every 8-16 weeks, or once every 6-16 weeks. In certain embodiments, the methods induce apoptosis of mast cells.

[0097] In particular embodiments, the subject is provided a single (e.g., high) dose of the anti-c-Kit antibody or fragment thereof, e.g., JSP191, of about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In certain embodiments, the methods induce apoptosis of mast cells.

[0098] In particular embodiments, the anti-c-Kit antibody or fragment thereof, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg patient weight, about 0.2 mg/kg to about 3.0 mg/kg, about 0.3 mg/kg to about 1.5 mg/kg, about 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 1.0 mg/kg, about 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 110 mg/kg, or about 120 mg/kg.

[0099] In particular embodiments, the anti-c-Kit antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂ is administered subcutaneously.

[00100] In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 10 weeks, about once every 12 weeks, about once every four months, or about once every six months. In some embodiments, the anti-CD117 antibody or fragment thereof is administered at a dose of 1 mg/kg to 2 mg/kg. In some embodiments, the anti-CD117 antibody or fragment thereof is administered at a dose of 1.2 mg/kg to 1.8 mg/kg. In some embodiments, the administration is subcutaneous, intravenous, or intramuscular injection. In a particular embodiment, the administration is subcutaneous. In some embodiments, a first dose of the administration results in mast cell count reduction in the subject for at least 1 week, 2 weeks, 3 weeks, or 4 weeks. In some embodiments, the anti-CD117 antibody or fragment thereof comprises an IgG Fc fragment not capable of activating antibody-dependent cellular cytotoxicity (ADCC).

[00101] Compositions and methods disclosed herein may be used to treat or prevent mast cell-related diseases and disorders, including but not limited to those involving chronically active mast cells, e.g., by administering an anti-c-kit antibody, e.g., JSP191, or a fragment thereof, e.g., a JSP191 (Fab')₂ fragment, to the subject. For example, in particular embodiments, the disclosed methods may be used to prevent or reduce an allergic response or to prevent recurrence of asthma exacerbation following allergen exposure. So, for example, the anti-c-kit antibody or antigen-binding fragment thereof may be administered to the subject prior to exposure to an allergen, or prior to re-exposure to an allergen.

[00102] Compositions and methods disclosed herein may be used prophylactically to inhibit or prevent a mast cell-related disease or disorder from developing, and they may be used therapeutically to treat a mast cell-related disease or disorder. In particular embodiments, a subject exposed to an allergen may be treated according to the disclosed methods to prevent, inhibit, or reduce an allergic response to the allergen.

[00103] While mast cell-related diseases and disorders include those wherein the mast cell itself is diseased or has a pathology, mast cell-related disease and disorders also include diseases and disorders that result in mast cell activation and/or release of cytokines, which can, in some instances, lead to inflammation and other problems. In certain embodiments, the compositions and methods disclosed herein are used to treat inflammation or inflammatory diseases and disorders. In certain embodiments, the compositions and methods disclosed herein are used to treat diseases and disorders associated with an innate immune response and/or an adaptive

immune response, including but not limited to autoimmune diseases, such as, e.g., autoimmune psoriasis.

[00104] Mast cell-related diseases and disorders include both IgE-mediated mast cell-related diseases and disorders and IgE-independent mast cell-related disease and disorders. In certain embodiments, both IgE-mediated mast cell-related diseases and disorders and IgE-independent mast cell-related disease and disorders can result in anaphylactoid reactions and/or allergic reactions. Non-limiting examples of IgE-mediated mast cell-related diseases and disorders include anaphylaxis, e.g., passive anaphylaxis, systemic anaphylaxis, passive systemic anaphylaxis, and allergic reactions, such as allergen-induced dermatitis (e.g., allergen-induced atopic dermatitis) and allergen-induced asthma (e.g., allergen-induced allergic asthma). Mast cell diseases and disorders may also result in allergic inflammation and tissue remodeling in asthma. Non-limiting examples of IgE-independent mast cell-related diseases and disorders include anaphylaxis (e.g., severe anaphylaxis), and C48/80-mediated anaphylactoid reactions. Anaphylactoid shock is a fatal hypersensitivity response caused by non-IgE-mediated mast cell activation.

[00105] Mast cells and/or their secretory products are involved in the pathogenesis of a variety of diseases and disorders. Examples of mast cell-related diseases and disorders include mast cell activation related disorders (MCAD), which are a heterogeneous group of conditions that may be associated with an increased number of mast cells and/or hyperactive mast cells. These disorders can vary in severity, but common symptoms include often severe reactions to insect stings, and in rare cases to foods or drugs. MCAD comprise clonal (e.g., mastocytosis) and nonclonal (idiopathic) variants. Clonal MC disorders (CMD) may be characterized by intrinsic MC defects, such as *KIT* mutation D816V, and/or expression of aberrant MC receptors, which may cause a “hyperactive” state of MCs leading to excessive release of mediators. Non-limiting examples of mast cell activation disorders include allergic disorders, mastocytosis, e.g., intestinal mastocytosis, such as intestinal mastocytosis following helminth infection, anaphylaxis, mast cell activation syndromes (MCAS), primary MCAS, secondary MCAS, mixed MCAS, and idiopathic MCAS. See, e.g., Gulen et al., *Immunology and Allergy Clinics*, Vol. 42, Issue 1, p45-63, February 2022.

[00106] Mast cells play a central role in many diseases and disorders, including but not limited to dermatological diseases, respiratory disease and disorders, gastrointestinal diseases and disorders, and many others. The methods disclosed herein may be used to treat any of these diseases or disorders. Non-limiting examples of mast cell-mediated diseases or disorders include urticaria, asthma, prurigo nodularis (PN), eosinophilic esophagitis (EoE),

mastocytosis, urticaria pigmentosa, anaphylaxis, endometriosis, interstitial cystitis, and mast cell activation syndrome (MCAS). In a particular example, the mast cell-mediated disease or disorder is chronic urticaria, such as chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CindU). Specific examples of dermatological diseases and disorders that may be treated according to the methods disclosed herein include, but are not limited to: urticarias (e.g., chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU)), dermatitis (e.g., allergic contact dermatitis and atopic dermatitis), alopecia (e.g., alopecia areata), bullous pemphigoid, prurigo nodularis, psoriasis, and rosacea. Specific examples of respiratory diseases and disorders that may be treated according to the methods disclosed herein include, but are not limited to: asthma, rhinitis (e.g., allergic rhinitis), aspirin exacerbated respiratory disease (AERD), chronic obstructive pulmonary disease (COPD), rhinosinusitis (e.g., chronic rhinosinusitis with nasal polyps (CRSwNP)), and pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis). Specific examples of gastrointestinal diseases and disorders that may be treated according to the methods disclosed herein include, but are not limited to: eosinophilic esophagitis (EoE), food allergy, oral immunotherapy, inflammatory bowel diseases (IBDs) (e.g., Crohn's disease and ulcerative colitis), and irritable bowel syndrome (IBS). Specific examples of other diseases and disorders that may be treated according to the methods disclosed herein include, but are not limited to: allergic conjunctivitis, age-related macular degeneration (AMD), alpha-1 antitrypsin deficiency, Alzheimer's disease, angioedema, celiac disease, dermatitis herpetiformis, graft versus host disease (e.g., chronic graft versus host disease), cystitis, endometriosis, fibromyalgia, hereditary alpha tryptasemia (HaT), anaphylaxis (e.g., idiopathic anaphylaxis), insulin-dependent diabetes mellitus, mast cell activation syndrome (MCAS), mast cell leukemia, mastocytosis (e.g., KIT negative), migraine, multiple sclerosis, pancreatitis (acute/chronic), arthritis (e.g., rheumatoid arthritis), and sickle cell disease (sickle crisis).

[00107] Mast cells are a key cellular target for a variety of inflammatory or autoimmune diseases that may be treated with the compositions and methods disclosed herein, including but not limited to, e.g., urticaria, chronic urticaria, chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), prurigo nodularis, eosinophilic esophagitis, asthma, e.g., allergic asthma, inflammatory bowel disease, fibrosis, scleroderma, systemic sclerosis.

[00108] In certain embodiments, the compositions and methods disclosed herein are used to treat inflammation or inflammatory diseases and disorders. In certain embodiments, the compositions and methods disclosed herein are used to treat diseases and disorders associated

with an innate immune response and/or an adaptive immune response, including but not limited to autoimmune diseases, such as, e.g., autoimmune psoriasis.

[00109] In particular embodiments, a subject exposed to an allergen may be treated according to the disclosed methods to prevent, inhibit, or reduce an allergic response to the allergen.

Chronic Urticaria

[00110] Chronic urticaria is a skin condition characterized by the presence of hives or welts that persist for more than six weeks. The condition can be caused by a variety of factors, including autoimmune disorders, infections, medications, and physical stimuli such as heat, cold, or pressure. There are multiple causes of chronic urticaria, such as infection, stress, or autoimmune diseases. In many cases, however, the cause is unknown. These cases are known as chronic idiopathic urticaria (CIU) or chronic spontaneous urticaria (CSU). Chronic urticaria is currently treated with medications to lessen the itch and relieve discomfort. There are also ways to prevent and improve symptoms at home, such as applying cold compresses to the affected skin. Stress management can help with treatment, as increased stress can worsen hives. Long-term hives can also cause more stress, leading to mental health challenges such as anxiety and depression. While current treatment options include antihistamines, corticosteroids, and immunosuppressants, they target the symptoms rather than the underlying diseases. Improved treatments are therefore needed.

[00111] Chronic spontaneous urticaria (CSU) affects about 1% of the population worldwide of all ages. It mainly affects young to middle-aged adults (disease onset at the age of approx. 30 to 50 years) and is more common in women than in men (Goncalo et al. 2021). CSU is defined by the presentation of pruritic wheals (hives) and/ or angioedema, which occur for more than six weeks without an identifiable specific trigger. The elevated lesions are accompanied by redness and intense continuous itching, which directly impacts many dimensions of a patient's quality of life. In many participants, CSU is of long duration, 5 to 7 years on average (Kolkhir et al. 2022). The manifestations have a strong effect on health-related quality of life, including sleep impairment, diminished physical and emotional well-being and poor performance at school or work.

[00112] CSU is associated with considerable healthcare utilization and economic burden, including both regular and unanticipated healthcare visits, costs due to laboratory expenses and indirect costs due to the absence from work or reduced efficiency. It's well-characterized that greater disease severity is associated with greater impact on quality of life (Armstrong 2023, Maurer 2017, Vietri 2015). In a recent trial characterizing the HRQoL burden on CSU patients, the most significantly affected aspects of HRQoL in severe patients despite treatment

(UAS7 $\geq$ 16) were diminished physical well-being (pain/discomfort in ~70% of patients), emotional well-being (anxiety/depression in ~55% of patients), sleep impairment (~50% of patients) and poor work performance (~20% of patients missed at least 1 hour of work in past 7 days due to CSU symptoms) (Maurer 2017).

[00113] Although the cause of CSU is not fully understood yet, several molecular mechanisms leading to mast cell activation have been described to date. Activation and degranulation of skin mast cells and the release of histamine or other mediators (e.g., tryptase, TNF, different interleukins) are the key drivers of the development of symptoms.

[00114] Current standard-of-care of CSU includes oral H1-antihistamines, as well as second- and third line therapies, i.e., omalizumab and cyclosporine, respectively (Metz et al. 2021; Kolkhir et al. 2022; Zuberbier et al. 2022). However, about 40-50% of patients have uncontrolled symptoms, despite being administered doses higher than FDA-approved doses (Maurer 2017, Guillén-Aguinaga 2016), and more than 25% of cases are resistant to antihistamines, even at higher doses. Omalizumab, an anti-IgE antibody, was licensed as a treatment agent of CSU in antihistamine-refractory participants and may be used as an add-on therapy to antihistamines. However, less than 50% of patients have complete symptom resolution (Maurer 2013, Saini 2015). In addition to the incomplete symptom control, omalizumab has a boxed warning for anaphylaxis, deeming some patients ineligible (Xolair Prescribing Information 2023). Omalizumab's risk of allergic reaction is not dissimilar to other FDA approved biologics for dermatologic conditions, including dupilumab for atopic dermatitis, which holds a warning for hypersensitivity reactions (Dupixent Prescribing Information 2022). Altogether, there is a significant group of moderate-to-severe CSU patients who remain symptomatic despite treatment with omalizumab or who cannot tolerate omalizumab. The development of further novel therapies is, therefore, strongly recommended.

[00115] In certain embodiments, methods disclosed herein are used to treat patients with CSU, e.g., optionally who remain symptomatic despite treatment with antihistamine or who cannot tolerate antihistamine. In particular embodiments, the antihistamine is an H1-antihistamine. In certain embodiments, methods disclosed herein are used to treat patients with CSU, e.g., optionally who remain symptomatic despite treatment with omalizumab or who cannot tolerate omalizumab (Xolair®). In certain embodiments, methods disclosed herein are used to treat patients with CSU who are Xolair®-naive and/or Xolair®-failed.

[00116] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing CSU in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit IgG

antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg, or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂). In certain embodiments, the patients have previously shown inadequate response to H1-antihistamines and/or omalizumab or who cannot tolerate omalizumab, and in certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every ten weeks, about once every 12 weeks, about once every four months, or about once every six months. Optionally, the subject is administered one or more doses (e.g., a single dose) of about 1 mg/kg body weight to about 4 mg/kg body weight, e.g., about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, or about 4 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally. In certain embodiments, the antibody is administered subcutaneously.

[00117] In one embodiment of treating, inhibiting, or preventing CSU, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is

administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart. In certain embodiments, the human subject is symptomatic despite treatment with H1-antihistamines and/or omalizumab or cannot tolerate omalizumab.

[00118] In certain embodiments, the subject is administered a single dose of the anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein the dose is any of those disclosed herein, including those disclosed for treatment regimen comprising administering two or more doses.

[00119] In particular embodiments, the anti-c-Kit antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, is administered as one or more doses of about 0.2 to about 3.0 mg/kg patient weight or about 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 40 mg to about 200 mg, e.g., about 80 mg, about 90 mg/kg, about 100 mg, about 110 mg, or about 120 mg. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof (e.g., a JSP191 (Fab')₂), is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In particular embodiments, the anti-c-Kit antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, is administered subcutaneously.

Chronic Inducible Urticaria (CIndU)

[00120] Chronic inducible urticaria (CIndU) is a subtype of urticaria characterized by the recurrence of symptoms (itchy wheals and/or angioedema) recurring for longer than six weeks. Similar to CSU, CIndU is characterized by development of hives and/or angioedema and redness in the skin. Unlike CSU, the trigger for CIndU patients can be diagnosed by assessment of various common provocations such as cold, heat, pressure, vibration and others. The two most common forms of CIndU are symptomatic dermographism (SD) and cold contact urticaria (ColdU). CIndU is thought to affect over one million patients in the United States, France, Germany, Italy, Spain and the United Kingdom. Approximately 40% of these patients'

CIndU is not controlled by first line anti-histamines and these patients could be eligible for biologic therapy depending on disease severity.

[00121] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing CIndU in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), e.g., wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00122] In certain embodiments, the subject is administered a single dose. In certain embodiments, the subject is administered a single dose of the anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein the dose is any of those disclosed herein, including those disclosed for treatment regimens comprising administering two or more doses.

[00123] In certain embodiments, the subject has cold urticaria and/or symptomatic dermatographism.

[00124] In one embodiment of treating, inhibiting, or preventing CIndU, a human subject, e.g., a human adult, is subcutaneously administered one dose of JSP191, wherein the dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 80 mg,

about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191. In particular embodiments, the subject is administered at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In particular embodiments, the subject has a diagnosis of CIndU, e.g., ColdU or SD, despite the use of H1-antihistamines.

[00125] In one embodiment of treating, inhibiting, or preventing CIndU, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

[00126] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about

3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg to about 150 mg, about 40 mg to about 200 mg, e.g., about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, or about 120 mg. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

Prurigo Nodularis

[00127] Prurigo Nodularis is also a disease that manifests in the skin. Patients develop severe itch and firm bumps on the skin, called nodules, that may lead to loss of sleep and bleeding due to scratching. Degranulation of mast cells in the skin is thought to trigger peripheral sensory neurons in the skin leading to itch. Various medications are used to treat Prurigo Nodularis including anti-itch creams and topical steroids. For cases that remain uncontrolled physicians may prescribe anti-histamines or biologics such as dupilumab. PN is also known as Hyde prurigo nodularis, Picker's nodules, atypical nodular form of neurodermatitis circumscripta, lichen corneus obtusus.

[00128] The cause of prurigo nodularis is unknown, although other conditions may induce PN. PN has been linked to Becker's nevus, linear IgA disease, an autoimmune condition, liver disease and T cells. Systemic pruritus has been linked to cholestasis, thyroid disease, polycythaemia rubra vera, uraemia, Hodgkins disease, HIV and other immunodeficiency diseases. Internal malignancies, liver failure, kidney failure, and psychiatric illnesses have been considered to induce PN, although more recent research has refuted a psychiatric cause for PN. Patients report an ongoing battle to distinguish themselves from those with psychiatric disorders, such as delusions of parasitosis and other psychiatric conditions.

[00129] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing Prurigo nodularis in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5

mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00130] In certain embodiments, the subject is administered a single dose. In certain embodiments, the subject is administered a single dose of the anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein the dose is any of those disclosed herein, including those disclosed for treatment regimens comprising administering two or more doses.

[00131] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg to about 150 mg, about 40 mg to about 200 mg, e.g., about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00132] In certain embodiments, the subject is administered a single dose. In certain embodiments, the subject is administered a single dose of the anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein the dose is any of those disclosed herein, including those disclosed for treatment regimen comprising administering two or more doses.

[00133] In one embodiment of treating, inhibiting, or preventing PN, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg,

about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Eosinophilic Esophagitis

[00134] Eosinophilic esophagitis is an immune disorder leading to build up of eosinophils in the esophagus and causes difficulty in eating, chronic reflux and/or the sensation of heartburn. Along with the buildup of eosinophils, there is typically buildup of other immune cells in the affected area including mast cells, basophils and lymphocytes. In healthy individuals, the esophagus is typically devoid of eosinophils. In EoE, eosinophils migrate to the esophagus in large numbers. When a trigger food is eaten, the eosinophils contribute to tissue damage and inflammation. Symptoms include swallowing difficulty, food impaction, vomiting, and heartburn. Symptoms include swallowing difficulty, food impaction, vomiting, and heartburn. Patients may be treated with changes to diet, use of proton pump inhibitors, antihistamines and dupilumab.

[00135] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing eosinophilic esophagitis in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), or about 30 mg to about 150 mg, about 40 mg to

about 200 mg, e.g., about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg, optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00136] In certain embodiments, the subject is administered a single dose. In certain embodiments, the subject is administered a single dose of the anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein the dose is any of those disclosed herein, including those disclosed for treatment regimens comprising administering two or more doses.

[00137] In one embodiment of treating, inhibiting, or preventing EoE, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months,

about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Asthma

[00138] Asthma is a long-term inflammatory disease of the airways of the lungs, characterized by variable and recurring symptoms, reversible airflow obstruction, and easily triggered bronchospasms. Symptoms include episodes of wheezing, coughing, chest tightness, and shortness of breath. These may occur a few times a day or a few times per week. Depending on the person, asthma symptoms may become worse at night or with exercise. Asthma is thought to be caused by a combination of genetic and environmental factors. Environmental factors include exposure to air pollution and allergens. Other potential triggers include medications such as aspirin and beta blockers. Diagnosis is usually based on the pattern of symptoms, response to therapy over time, and spirometry lung function testing. Asthma is classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate. It may also be classified as atopic or non-atopic, where atopy refers to a predisposition toward developing a type 1 hypersensitivity reaction.

[00139] Methods and compositions disclosed herein may be used to treat asthma. Mast cells are distributed throughout multiple compartments in the lung. Mast cells release/activate various mediators that drive asthma pathophysiology. Early phase in asthma is driven by mast cell degranulation (and release of histamine, prostaglandins, leukotrienes, IL-5, IL-13, IL-4 and CXCR2, and may also drive the late phase recruitment of other cell types to the lung. Current therapeutic strategies in asthma target specific upstream (IgE, TSLP) or downstream mediators (IL-5, IL-4/IL-13) but do not broadly inhibit mast cells. Methods and compositions disclosed herein may be used to treat asthma, and in particular embodiments, e.g., to induce mast cell apoptosis, inhibit release of mediators that drive asthma pathophysiology, and/or inhibit recruitment of other cell types to the lungs.

[00140] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing asthma or an allergic reaction in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein each dose comprises about 0.2 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 2.0 mg/kg, about 0.8 mg/kg, about 1.0 mg/kg, about 2.0 mg/kg, or about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 200 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), or about 30 mg to about 150 mg, about 40 mg to about 200 mg, e.g., about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg, optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every ten weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00141] In certain embodiments, the subject is administered a single dose. In certain embodiments, the subject is administered a single dose of the anti-c-kit antibody or antigen-binding fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein the dose is any of those disclosed herein, including those disclosed for treatment regimens comprising administering two or more doses.

[00142] In certain embodiments for inhibiting or preventing an allergic reaction or asthma, a subject is administered an anti-c-kit antibody or antigen-binding fragment thereof prior to an initial or subsequent contact with or exposure to an allergen, e.g., to prevent recurrence of asthma exacerbation following allergen exposure.

[00143] In particular embodiments, the anti-c-Kit antibody or fragment thereof, e.g., JSP191, is administered as one or more doses of about 0.2 to about 3.0 mg/kg patient weight or about 0.5

mg/kg to about 2.0 mg/kg, e.g., about 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 40 mg to about 200 mg, e.g., about 80 mg, about 90 mg/kg, about 100 mg, about 110 mg, or about 120 mg. In particular embodiments, the anti-c-Kit antibody or fragment thereof, e.g., JSP191, is administered subcutaneously.

[00144] In one embodiment of treating, inhibiting, or preventing asthma or an allergic reaction, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

[00145] In certain embodiments, methods and compositions disclosed herein are used to treat, inhibit, or prevent severe asthma, including severe asthma independent of Type 2 inflammation. Tryptase in bronchoalveolar lavage (BAL) and plasma are significantly elevated

in severe asthma as compared to healthy subjects or subjects with mild or moderate asthma. For example, normalized BAL tryptase levels may be greater than about 100 pg/mL or greater than about 125 pg/mL, and plasma tryptase levels may be greater than about 2000 pg/mL or greater than or about 4000 pg/mL. This elevated tryptase in severe asthma is independent of Type 2 inflammation. In particular embodiments, the methods and compositions disclosed herein are used to treat severe refractory asthma. They may be used to treat severe asthma with or without Type 2 inflammation.

[00146] Allergic asthma (e.g., allergen-induced allergic asthma) is a form of asthma triggered by specific allergens that leads to constriction of smooth muscles in the airways, cellular infiltration of various immune mediators and excess production of mucus. Allergic asthma may be associated with inflammation and tissue remodeling. Patients with allergic asthma may have an increased number of mast cells in the bronchi and may be responsive to agents that modulate mast cell response, including anti-histamines and anti-IgE monoclonal antibody therapy.

[00147] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing an allergic reaction, e.g., allergic asthma, in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally. In certain embodiments, the subject is administered a single dose. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.67 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg,

or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every ten weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00148] In particular embodiments, methods and compositions disclosed herein are used to treat, inhibit, or prevent any type of asthma, including asthma in patients who are not indicated for current biologic agents or remain refractory to them. In particular embodiments, the methods and compositions disclosed herein are used to treat moderate-to-severe (e.g., severe) asthma in patients refractory to one or more other treatment, e.g., refractory asthmatics with inadequate response to inhaled corticosteroids (ICS), long-acting β 2-agonists (LABA), and/or long-acting muscarinic antagonists (LAMA). Severe asthma is a potentially life-threatening inflammatory disorder characterized by persistent asthma symptoms, despite use of high doses of ICS and LABA/LAMA (2022 GINA Main Report. Global Initiative for Asthma – GINA). Asthma severity increases with age and the median age of severe asthma is 45-60 years (Ronnebjerg, L. et al. J Asthma Allergy. 2021;14:1105-1115 and Zein, JG et al., PLoS One. 2015; 10(7):e0133490). Approximately 300,000 patients currently receive biologic therapies in the US and EU. Selection of biologic therapy in severe asthma is based on disease biomarkers. Severe asthma may be divided into two classes: Type 2 High and Type 2 Low. Type 2 High include the following asthma endotypes: eosinophilic only asthma, eosinophilic and allergic asthma, and allergic only asthma (2022 GINA Main Report. Global Initiative for Asthma – GINA). Biomarkers for Type 2 High severe asthma include high FeNO in airways, high serum IgE, high serum periostin, high IFN- γ levels, and high blood/sputum eosinophils. Biomarkers for Type 2 Low severe asthma include neutrophil accumulation in the airways, low blood/sputum eosinophils, high TNF- α levels in the BAL, and high YKL-40 levels in the blood. In certain embodiments, type 2 low severe asthma patients have peripheral blood eosinophil counts < 300/ul. Patients with type 2 allergic only asthma or type 2 low asthma have limited treatment choices compared to patients with eosinophilic disease. For example, type 2 high eosinophilic only asthma patients may be treated with a variety of FDA approved therapies, including the following drugs and targets, e.g., Nucala® (mepolizumab; IL5), Cinqair® (reslizumab; IL5), Fasenra® (benralizumab; IL5), Dupixent® (dupilumab; IL4/IL13), and Tezspire® (tezepelumab; TSLP). Type 2 allergic only asthma patients may be

treated with FDA approved Xolair® (omalizumab; IgE) or Tezspire® (tezepelumab; TSLP), and Type 2 low asthma patients may be treated with Tezspire® (TSLP). In certain embodiments, methods and compositions disclosed herein may be used to treat any moderate-to-severe or severe asthma, such as, e.g., Type 2 High severe asthma and Type 2 Low severe asthma, including any form or endotype, e.g., type 2 high allergic only or type 2 low asthma. In particular embodiments, the treatment is provided subcutaneously.

Anaphylaxis

[00149] Anaphylaxis is as an acute, severe, systemic hypersensitivity reaction and represents an example of excessive MC activation resulting in the release of various mediators. Anaphylaxis can affect multiple organ systems and present with an array of symptoms. In certain embodiments, anaphylaxis comprises concurrent occurrence in at least two organ systems, which, in certain embodiments, include the cutaneous, gastrointestinal (GI), respiratory, and/or cardiovascular systems. Anaphylaxis comprises a heterogeneous group of conditions regarding the nature and route of exposure to triggers, organ involvement, severity, and time course. Anaphylaxis has a variety of causes. For example, food-induced systemic reaction is a leading cause of anaphylaxis in children, whereas venom- or drug-induced reactions account for most adult cases. From this perspective, severe anaphylaxis (SA) is a distinct anaphylaxis phenotype, which may involve hypotension and/or loss of consciousness. In particular embodiments, methods disclosed herein may be used to treat any type of anaphylaxis, e.g., IgE-mediated anaphylaxis and non-IgE anaphylaxis. A variety of drugs have been shown to cause IgE-mediated anaphylaxis, including, e.g., anti-anaphylaxis agents, chemotherapy agents, disease-modifying antirheumatic drugs (DMARDs), antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, radiocontrast agents, intraoperative agents, monoclonal antibodies, and others, such as, e.g., human IgG, lisinopril, morphine, and ondansetron. Examples of drugs implicated in non-IgE anaphylaxis include, e.g., fluoroquinolones, opioids, such as morphine and sufentanil, radiocontrast agents, atracurium, paclitaxel, and vancomycin. Many opioids, e.g., morphine, are potent histamine releasers producing a variety of haemodynamic changes and anaphylactoid reactions. Methods disclosed herein may be used to treat opioid-mediated or opioid receptor-mediated anaphylaxis.

[00150] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing anaphylaxis or an anaphylactoid reaction in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to

about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00151] In certain embodiments, the subject is administered a single dose.

[00152] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00153] In one embodiment of treating, inhibiting, or preventing anaphylaxis, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is

administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Mastocytosis

[00154] Mastocytosis, a type of mast cell disease, is a rare disorder affecting both children and adults caused by the accumulation of functionally defective mast cells (also called mastocytes) and CD34+ mast cell precursors. People affected by mastocytosis are susceptible to a variety of symptoms, including itching, hives, and anaphylactic shock, caused by the release of histamine and other pro-inflammatory substances from mast cells. Mastocytosis is characterized by excessive accumulation, proliferation, and activation of abnormal MCs in several organs, including the skin, bone marrow, and GI tract. Mastocytosis includes both cutaneous mastocytosis (CM) and systemic mastocytosis (SM) involving at least one extracutaneous organ. SM includes indolent SM (ISM) and more aggressive variants of the disease. Mastocytosis includes intestinal mastocytosis, e.g., intestinal mastocytosis following helminth infection.

[00155] Urticaria pigmentosa, also known as generalized eruption of cutaneous mastocytosis (childhood type), is the most common form of cutaneous mastocytosis. It is a rare disease caused by excessive numbers of mast cells in the skin that produce hives or lesions on the skin when irritated. Urticaria pigmentosa is characterized by excessive amounts of mast cells in the skin. Red or brown spots are often seen on the skin, typically around the chest, forehead, and back. These mast cells, when irritated (e.g., by rubbing the skin, heat exposure), produce too much histamine, triggering an allergic reaction that leads to hives localized to the area of

irritation, sometimes referred to as Darier's sign. Severe itching usually follows, and scratching the area only serves to further symptoms. Symptoms can be mild (flushing and hives that require no treatment), moderate (diarrhea, tachycardia, nausea/vomiting, headache, and fainting), or life-threatening (vascular collapse requiring emergency treatment and hospitalization).

[00156] The majority of urticaria pigmentosa cases are caused by a point mutation at amino acid 816 of the proto-oncogene c-Kit. Mutations in position 816 of c-Kit can result in a constant division signal being sent to the mast cells, resulting in abnormal proliferation. Different mutations have been linked to different onset times of the disease. For example, the Asp816Phe and Asp816Val mutations (the aspartate normally at position 816 in the c-kit protein has been replaced with phenylalanine or valine respectively) have been associated with early manifestation of the disease.

[00157] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing mastocytosis, e.g., urticaria pigmentosa, in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00158] In certain embodiments, the subject is administered a single dose.

[00159] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the

patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00160] In one embodiment of treating, inhibiting, or preventing mastocytosis, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Mast Cell Activation Syndrome

[00161] MC activation syndrome (MCAS) is a disorder of MC activation with various causes all resulting in severe, recurrent, and episodic symptoms due to systemic MC mediator release. Patients with MCAS often present with symptoms of anaphylaxis. However, neither all anaphylaxis fulfill diagnostic criteria of MCAS nor do all MCAS episodes reach the severity of anaphylaxis. MC activation can manifest as a less severe and/or chronic condition.

[00162] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing MCAS in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00163] In certain embodiments, the subject is administered a single dose.

[00164] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00165] In one embodiment of treating, inhibiting, or preventing MCAS, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Fibrosis

[00166] Methods disclosed herein may be used to treat fibrotic diseases and disorders. As used herein the term “fibrotic disease or disorder” refers to conditions involving fibrosis in one or more tissues. As used herein the term “fibrosis” refers to aberrant formation or development of excess fibrous connective tissue in an organ or tissue as a reactive process, as opposed to formation of fibrous tissue as a normal constituent or healing of an organ or tissue. Fibrosis is characterized by fibroblast accumulation and collagen deposition in excess of normal

deposition in any particular tissue. As used herein the term “fibrosis” includes aberrant healing, involving mesenchymal-fibroblast cell transformation, excessive fibroblast proliferation, activity and deposition of collagens and other extracellular matrix proteins. Compositions and methods disclosed herein may also be used to treat atherosclerosis. Vascular fibrosis, characterized by reduced lumen diameter and arterial wall thickening attributable to excessive deposition of extracellular matrix (ECM), is associated with many clinical diseases and pathological progresses including atherosclerosis.

[00167] Mast cell number and mast cell mediators are significantly elevated in most human fibrotic diseases, including but not limited to, idiopathic pulmonary fibrosis (IPF) and scleroderma. Differential mast cell phenotypes are detected in some scleroderma patients and in the Tsk mouse model of scleroderma. An aggressive systemic form of mastocytosis may be characterized by myelofibrosis indicating that mast cells can be effector cells in fibrosis.

[00168] Examples of mast cell associated fibrotic diseases include, but are not limited to, pathological fibrosis or scarring (including endocardial sclerosis), idiopathic interstitial fibrosis, interstitial pulmonary fibrosis, perimuscular fibrosis, Symmers' fibrosis, pericentral fibrosis, hepatitis, dermatofibroma, biliary cirrhosis, alcoholic cirrhosis, acute pulmonary fibrosis, idiopathic pulmonary fibrosis, acute respiratory distress syndrome, kidney fibrosis/glomerulonephritis, kidney fibrosis/diabetic nephropathy, scleroderma/systemic, scleroderma/local, keloids, hypertrophic scars, severe joint adhesions/arthritis, myelofibrosis, corneal scarring, cystic fibrosis, muscular dystrophy (duchenne's), cardiac fibrosis, muscular fibrosis/retinal separation, esophageal stricture and payronles disease. Further fibrotic disorders may be induced or initiated by surgery, including scar revision/plastic surgeries, glaucoma, cataract fibrosis, corneal scarring, joint adhesions, graft vs. host disease, tendon surgery, nerve entrapment, dupuytren's contracture, OB/GYN adhesions/fibrosis, pelvic adhesions, peridural fibrosis, restenosis. It is also contemplated that fibrotic conditions where deposition of fibronectin is a causative factor can be treated according to the invention. Idiopathic pulmonary fibrosis, bleomycin lung, cystic fibrosis, and glomerular nephropathy, including disease characterized by Fn deposits in the kidneys ultimately leading to renal failure are examples of conditions which can also be treated in accordance with the present invention. Inflammation involving activation of the immune system and where mast cells secrete inflammatory cytokines such as TNF, and can activate and directly interact with lymphocytes can also be treated in accordance with the present invention.

[00169] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing fibrosis or a fibrotic disease or disorder in a mammalian, e.g., human, subject, the

method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00170] In certain embodiments, the subject is administered a single dose.

[00171] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00172] In one embodiment of treating, inhibiting, or preventing fibrosis or a fibrotic disease, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg,

about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Allergic Diseases and Disorders

[00173] The role of mast cells in allergic diseases has been clinically validated by drugs that block mast cell specific mediators such as histamine and corticosteroids, which among their activities cause mast cell apoptosis. Additional mast cell-related diseases include, e.g., histamine-mediated allergic reactions that can be treated by inhibiting chemokine-induced mast cell and basophil degranulation and release of histamine. Additional examples of mast cell associated disorders or diseases which may be effectively treated with the subject methods and compositions also include, but are not limited to, contact dermatitis, atopic dermatitis, allergic dermatitis (e.g., allergen-induced atopic dermatitis), allergic asthma, eczematous dermatitis, dermatitis caused by insect bites or stings, and allergic diarrhea.

[00174] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing an allergic disease or disorder in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody

or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00175] In certain embodiments, the subject is administered a single dose.

[00176] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00177] In one embodiment of treating, inhibiting, or preventing allergies or allergic diseases, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks

apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

[00178] In certain embodiments for inhibiting or preventing an allergic reaction, a subject is administered an anti-c-kit antibody or antigen-binding fragment thereof prior to an initial or subsequent contact with or exposure to an allergen, e.g., to prevent an allergic reaction to the allergen exposure.

Inflammatory Bowel Disease (IBD)

[00179] Inflammatory bowel disease (IBD) is a chronic inflammatory condition that primarily affects the gastrointestinal tract. There are two main types of IBD: Crohn's disease and ulcerative colitis. Crohn's disease can affect any part of the digestive tract; however, it most commonly affects the small intestine and the beginning of the large intestine (colon). The inflammation in Crohn's disease is characterized by transmural involvement, meaning it affects all layers of the intestinal wall, potentially causing the formation of ulcers, strictures, and fistulas. In contrast, ulcerative colitis primarily affects the colon and the rectum. The inflammation in ulcerative colitis is usually limited to the inner lining of the colon, known as the mucosa. It typically begins in the rectum and can spread to involve different parts of the colon. Both Crohn's disease and ulcerative colitis are believed to result from an inappropriate immune response in genetically susceptible individuals.

[00180] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing an IBD in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about

250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00181] In certain embodiments, the subject is administered a single dose.

[00182] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00183] In one embodiment of treating, inhibiting, or preventing IBD, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about

240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Other Mast Cell-mediated Diseases and Disorders

[00184] Other mast cell-related indications suitable for treatment by the methods and compositions of the invention include pulmonary inflammatory conditions in interstitial lung diseases for example sarcoidosis, neonatal respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), and conditions characterized by an elevation in serum PLA2 activity, such as adult RDS (ARDS). Others include arthritis, including both osteoarthritis and rheumatoid arthritis, anaphylaxis, endometriosis, interstitial cystitis (IC), septic shock, pancreatitis, collagen vascular diseases, acute renal failure, peritonitis, and autoimmune uveitis. Studies also suggest that mast cells participate in the pathophysiology of multiple sclerosis. Thus, it is contemplated that the methods and compositions of the invention are suitable for treatment or amelioration of the morbidity associated with multiple sclerosis.

[00185] Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways with progressive and irreversible decline in lung function caused by airway obstruction and destruction of parenchyma. Three pathological disorders, including chronic bronchitis, small airway disease, and emphysema, existing either separately or in combination culminate in COPD. Chronic inflammation is the hallmark of COPD, involving the interplay of a wide variety of cells in the lung microenvironment. Macrophages, neutrophils, dendritic cells, and CD8⁺ T-lymphocytes are generally considered the key inflammatory cells involved in COPD. However, an increase in the density of mast cells of the MC_{TC} subtype has been reported in the

alveolar parenchyma and airway smooth muscle in COPD. Thus, methods disclosed herein may be used to treat COPD. Other mixed inflammatory or allergic airway inflammatory disorders may also be treated.

[00186] Anaphylaxis is a serious, potentially fatal allergic reaction and medical emergency that is rapid in onset and requires immediate medical attention regardless of use of emergency medication on site. It typically causes more than one of the following: an itchy rash, throat closing due to swelling that can obstruct or stop breathing; severe tongue swelling that can also interfere with or stop breathing; shortness of breath, vomiting, lightheadedness, loss of consciousness, low blood pressure, and medical shock. Common causes include allergies to insect bites and stings, foods, sulfites, medications, general anaesthetic, contrast agents, or latex. The mechanism involves the release of inflammatory mediators in a rapidly escalating cascade from certain types of white blood cells triggered by either immunologic or non-immunologic mechanisms.

[00187] Endometriosis is a disease of the female reproductive system in which cells in the layer of tissue that normally covers the inside of the uterus grow outside the uterus. Lesions can be found on ovaries, fallopian tubes, tissue around the uterus and ovaries (peritoneum), intestines, bladder, and diaphragm; it may also occur in other parts of the body. Symptoms include pelvic pain, heavy and painful periods, pain with bowel movements, painful urination, pain during sexual intercourse and infertility. Clinical data demonstrates a disproportionate mast cell infiltrate into endometriotic lesions suggestive that mast cells are a key driver of symptoms including chronic pain.

[00188] Interstitial cystitis (IC), a type of bladder pain syndrome (BPS), is chronic pain in the bladder and pelvic floor. Symptoms include feeling the need to urinate right away, needing to urinate often, and pain with sex. The cause of IC/BPS is not well understood. Evidence from clinical and laboratory studies confirms that mast cells play a central role in IC/BPS possibly due to their ability to release histamine and cause pain, swelling, scarring, and interfere with healing.

[00189] These and other mast cell-related diseases and disorders may be treating using the agents and dosing regimens disclosed herein.

[00190] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing any mast cell-related disease or disorder in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to

about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally.

[00191] In certain embodiments, the subject is administered a single dose.

[00192] In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00193] In one embodiment of treating, inhibiting, or preventing a mast cell-related disease or disorder, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 40 mg, about 60 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of

the two or more doses is administered to the subject at least four weeks apart, at least six weeks apart, at least eight weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about six weeks to about six months, about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 40 mg, at least or about 60 mg, at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

Dosage and Administration

[00194] According to particular embodiments related to treatment of mast cell-related diseases or disorders, the anti-c-kit antibody treatments described herein may be administered in dosing regimens that deplete mast cells, e.g., via apoptosis. Any of the dosing regimens disclosed herein or described herein for another mast cell-related disease may be used for other mast cell-related diseases and disorders.

[00195] In some embodiments, a subject in need thereof is administered an anti-c-kit antibody in a dose of about 0.01 mg/kg to about 20 mg/kg.

[00196] In particular embodiments, the subject is administered a single, high dose of the anti-c-Kit antibody, e.g., JSP191, of about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In some embodiments, the anti-c-kit antibody is any of SR-1, JSP191, MGTA-117, FSI-174, CDX-0159, 8D7, K45, 104D2, CK6, AB249, YB5.B8, AF-2-1, AF11, AF12, AF112, AF-3, AF-1-1, NF, NF-2-1, NF11, NF12, NF112, NF-3, HF11, HF12, and HF112 administered in a dose of about 0.01 mg/kg to about 20 mg/kg subject body weight.

[00197] In some embodiments, the anti-c-kit antibody, e.g., briquilimab, is administered in a dose of about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg,

about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2.0 mg/kg, about 2.25 mg/kg, about 2.5 mg/kg, about 2.75 mg/kg, about 3.0 mg/kg, about 3.25 mg/kg, about 3.5 mg/kg, about 3.75 mg/kg, about 4.0 mg/kg, about 4.5 mg/kg, about 5.0 mg/kg, about 5.5 mg/kg, or about 6.0 mg/kg. In certain embodiments, the anti-c-Kit antibody is administered at a dose of about 0.01 mg/kg to about 20 mg/kg, about 0.1 mg/kg to about 10 mg/kg, about 0.1 mg/kg to about 5.0 mg/kg, about 0.1 mg/kg to about 4 mg/kg, about .5 mg/kg to about 5.0 mg/kg, about .5 mg/kg to about 4.0 mg/kg, about .5 mg/kg to about 3.0 mg/kg, or about .5 mg/kg to about 2.0 mg/kg. In particular embodiments, JSP191 is administered at any of these dosages. In particular embodiments, the subject is administered a single, high dose of the anti-c-Kit antibody, e.g., JSP191, of about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, CDX0158 or CDX0159 is administered at any of these dosages. In particular embodiments, FSI-174 is administered at any of these dosages.

[00198] In some embodiments, a subject in need thereof is administered a single dose of an anti-c-kit antibody as described herein. In some embodiments the subject is administered two or more doses of the anti-c-kit antibody.

[00199] In particular embodiments of methods disclosed herein, including, e.g., depleting mast cells or treating a mast cell-related disease or disorder, the subject is administered one or more doses of about 10 mg to about 1000 mg, about 20 mg to about 1000 mg, about 20 mg to about 500 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, or about 20 mg to about 300 mg of the anti-c-kit antibody, e.g., JSP191. In some embodiments, the subject is administered a dose of about 25 mg to about 250 mg, about 50 mg to about 240 mg, about 100 mg to about 250 mg, about 50 mg to about 250 mg, about 100 mg to about 200 mg, about 80 mg to about 180 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, or about 300 mg of the anti-c-kit antibody, e.g., JSP191. In some embodiments, the subject is administered a dose of about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg of the anti-c-kit antibody, e.g., JSP191.

[00200] In certain embodiments, any of the mast cell-related diseases or disorders may be treated by subcutaneously administering to a human subject in need thereof two or more doses of JSP-191, wherein each dose comprises about 40 mg to about 360 mg of JSP-191, about 40 mg to about 240 mg of JSP-191, or about 120 mg to about 240 mg of JSP191, e.g. about 40 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg, wherein each of the two or more doses of JSP-191 are administered at least eight weeks apart, e.g., once about every eight weeks to about six months, or once about every eight weeks to about four months, or once about every three months to every six months, or once about every eight weeks.

[00201] In some embodiments, a subject is administered an anti-c-kit antibody, e.g., JSP-191, in a dosing regimen of about every week, about every 2 weeks, about every 3 weeks, about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, about every 12 weeks, about every 13 weeks, about every 14 weeks, about every 15 weeks, about every 16 weeks, about every 17 weeks, about every 18 weeks, about every 19 weeks, about every 20 weeks, about once per month, about once every two months, about once every three months, about once every four months, about once every six months, or about once a year.

[00202] In some embodiments, a subject is administered two or more doses of the anti-c-kit antibody, e.g., JSP191, wherein each dose is about 20 mg to about 300 mg of the anti-c-kit antibody or about 50 mg to about 300 mg of the anti-c-kit antibody, or about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg of the anti-c-kit antibody. In some embodiments, one of the two or more doses is administered every two weeks to six months, every four weeks to four months, every two to 16 weeks, every four to twelve weeks, every six to ten weeks, every seven to 9 weeks, about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, about every 12 weeks, about every 16 weeks, about every four months, about every six months, or about every year, optionally wherein the time interval between each dose varies. In some embodiments, each dose of the anti-c-kit antibody, e.g., JSP191, is about 35 mg to about 240 mg, about 35 mg to about 180 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, or about 240 mg of the anti-c-kit antibody, e.g., JSP191. In some embodiments, the subject is administered a dose of about 35 mg, about 80 mg, about 100 mg, about 180 mg, or about 240 mg of the anti-

c-kit antibody, e.g., JSP191. In some embodiments, a subject is administered a dose of about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg of the anti-c-kit antibody, e.g., JSP191, about every eight weeks.

[00203] In some embodiments, a subject is administered two or more doses of the anti-c-kit antibody, e.g., JSP191. In some embodiments, one of the two or more doses is administered every two to 16 weeks, every four to twelve weeks, every six to ten weeks, every seven to nine weeks, about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, about every 8 weeks, about every 9 weeks, about every 10 weeks, about every 11 weeks, about every 12 weeks, about every 16 weeks, about every four months, about every six months, or about every year, optionally wherein the time interval between each dose varies.

[00204] In some embodiments, a subject is administered two or more doses of the anti-c-kit antibody, e.g., JSP-191, wherein the time interval between administration of each of the doses is least eight weeks, at least ten weeks, at least twelve weeks, at least sixteen weeks, at least six months, or at least a year, optionally wherein the time interval between each dose varies. In some embodiments, the maximum time interval between administration of each of the doses is about 8 weeks, about 12 weeks, about four months, about six months, or about a year. In some embodiments, each dose is about 20 mg to about 275 mg of the anti-c-kit antibody or about 50 mg to about 300 mg of the anti-c-kit antibody, e.g. about 35 mg to about 180 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 300 mg, or about 360 mg of the anti-c-kit antibody, e.g., JSP191. In some embodiments, the subject is administered a dose of about 35 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg or about 360 mg of the anti-c-kit antibody, e.g., JSP191.

[00205] In some embodiments, the subject is administered a dosing regimen of an anti-c-kit antibody wherein the time interval between each dose varies, e.g., a subject may be administered a dose about every week for about 4 weeks, followed by a dose about every 2 weeks for about 8 weeks, and combinations thereof. In some embodiments, a subject may be administered a dose about every 8-12 weeks.

[00206] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing a mast cell disease or disorder in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a

monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg, or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂). In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., JSP191 or a JSP191 (Fab')₂, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every ten weeks, about once every 12 weeks, about once every four months, or about once every six months. Optionally, the subject is administered one or more doses (e.g., a single dose) of about 1 mg/kg body weight to about 4 mg/kg body weight, e.g., about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, or about 4 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally. In certain embodiments, the antibody is administered subcutaneously.

[00207] In one embodiment of treating mast cell-related diseases or disorders, a human subject, e.g., a human adult, is subcutaneously administered two or more doses of JSP191, wherein each dose is about 40 mg to about 500 mg, about 40 mg to about 360 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191, and wherein each of the two or more doses is administered to the subject at least four weeks apart, at least 8 weeks apart, at least twelve weeks apart, at least four months apart, or at least six months apart, e.g., with an interval between each of the two or more doses of between about eight weeks to about six months, about eight weeks to about four months, about twelve weeks to about six months, about twelve weeks to about four months, about 8 weeks, about 9 weeks, about 10 weeks, about 12 weeks, about four months, or about six months, optionally wherein the time interval between each dose varies. In particular embodiments, the subject is administered at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191. In one embodiment, the subject

is administered two or more doses of JSP191, wherein each dose is about 80 mg to about 280 mg, optionally about 80 mg, about 120 mg, about 180 mg, or about 240 mg, and the doses are administered between about eight weeks and about four months apart, or between about eight weeks and six months apart, optionally about eight weeks or about twelve weeks apart.

[00208] In some embodiments of treating mast cell-related diseases and disorders, a human subject, e.g., a human adult, is subcutaneously administered one dose of JSP191, wherein the dose is about 40 mg to about 500 mg, about 40 mg to about 360 mg, about 40 mg to about 400 mg, about 40 mg to about 300 mg, about 40 mg to about 200 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg, about 50 mg to about 200 mg, about 60 mg to about 500 mg, about 60 mg to about 400 mg, about 60 mg to about 300 mg, about 60 mg to about 200 mg, about 80 mg to about 500 mg, about 80 mg to about 400 mg, about 80 mg to about 300 mg, about 80 mg to about 200 mg, about 100 mg to about 500 mg, about 100 mg to about 400 mg, about 100 mg to about 300 mg, about 100 mg to about 200 mg, about 120 mg to about 500 mg, about 120 mg to about 400 mg, about 120 mg to about 300 mg, about 120 mg to about 200 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of JSP191. In particular embodiments, the subject is administered at least or about 80 mg, at least or about 100 mg, at least or about 120 mg, at least or about 160 mg, at least or about 180 mg, at least or about 200 mg, or at least or about 240 mg of JSP191.

[00209] In certain embodiments, the subject is administered a single, high dose of the anti-c-Kit antibody, e.g., JSP191, of about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg, e.g., intravenously or subcutaneously.

[00210] In certain embodiments, the disclosure provides for a method of treating a mast cell-related disease or disorder, such as any of the mast cell-related diseases or disorders disclosed herein, the method comprising providing to a subject having a mast cell-related disease or disorder one or more doses of JSP-191, where each dose is about 50 mg to about 500 mg or about 80 to about 280 mg, e.g., about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg. In particular embodiments, two or more doses of JSP-191 are administered to the subject, wherein each of the doses is administered between about four weeks and about one year apart, between about eight weeks and about one year apart, between about eight weeks and about six months apart, between about eight weeks and about four months apart, or between about eight weeks and twelve weeks apart. In particular embodiments, the doses are

administered intravenously or subcutaneously. In particular embodiments, the disease being treated is CSU. In particular embodiments, the disease being treated is anaphylaxis or a specific form thereof, e.g., opioid-mediated anaphylaxis.

[00211] In some embodiments, the dosing regimen is continued for about or at least a month, about or at least 6 months, about or at least a year, about or at least 2 years, about or at least 3 years, or about or at least 5 years. In some embodiments, the dosing regimen is continued until the subject is disease-free. In some embodiments wherein a subject is administered two or more doses of the anti-c-kit antibody, the subject's disease symptoms are monitored following each dose, and the subject is administered another dose when symptoms of the disease recur or become more prominent.

[00212] According to embodiments of the methods disclosed herein, monotherapy treatment with the anti-c-kit antibody is sufficient, and the subject does not need to be treated with another therapeutic agent for the disease being treated. In other embodiments, the subject is treated with the anti-c-kit antibody in combination with immunotherapy for treatment of the disease being treated. In some embodiments, the subject is treated with the anti-c-kit antibody in combination with anti-histamines. In some embodiment, the subject is treated with the anti-c-kit antibody in combination with an immunosuppressive agent, such as, e.g., cyclosporine A or a glucocorticoid, e.g., repeated administration of oral glucocorticoids.

[00213] In some embodiments, the anti-c-kit antibody therapy (or combination therapy) may be delivered orally, subcutaneously, intravenously, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, vaginally, rectally, or intraocularly. In some embodiments, the anti-c-kit antibody, e.g., JSP191, is administered locally or systemically, e.g., intravenously or subcutaneously. In some embodiments, an anti-c-kit antibody is delivered to the skin, e.g., by local injection or application, or subcutaneously.

[00214] In certain embodiments, the disclosure provides a method for treating, inhibiting, or preventing a mast cell-related disease or disorder, including but not limited to any of the diseases or disorders disclosed herein, in a mammalian, e.g., human, subject, the method comprising administering to the subject one or more therapeutically effective doses of a monoclonal anti-c-kit antibody (e.g., JSP191) or fragment thereof (e.g., a JSP191 (Fab')₂), wherein each dose comprises about 30 mg to about 250 mg, about 30 mg to about 300 mg, about 40 mg to about 300 mg, about 50 mg to about 300 mg or about 50 mg to about 600 mg of the anti-c-kit antibody or fragment thereof (e.g., a JSP191 (Fab')₂), optionally wherein the subject is administered a single dose of about 0.3 mg/kg to about 3.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 1 mg/kg to about 5 mg/kg, about

0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg. In particular embodiments, the antibody or fragment thereof is administered systemically, e.g., intravenously (i.v.), subcutaneously (s.c.), or intraperitoneally (i.p.), or locally. In certain embodiments, the subject is administered a single dose. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg to about 200 mg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered subcutaneously.

[00215] In embodiments, the disclosure provides methods for treating, inhibiting, or preventing a mast cell disorder in a subject, e.g., any of those disclosed herein, e.g., CSU or CIndU, comprising administering to the subject a an anti-CD117 antibody, e.g., JSP191, or fragment thereof, at a therapeutically effective dose or dosing regimen.

[00216] In one embodiment, the amount of the antibody (e.g., JSP191) or antigen binding fragment thereof administered is 0.5 mg/kg to 5 mg/kg. In some embodiments, the amount administered is at least 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1.0 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0 mg/kg, 3.5 mg/kg, 4.0 mg/kg, or 4.5 mg/kg. In some embodiments, the amount administered is not greater than 5 mg/kg, 4.5 mg/kg, 4.0 mg/kg, 3.5 mg/kg, 3.0 mg/kg, 2.9 mg/kg, 2.8 mg/kg, 2.7 mg/kg, 2.6 mg/kg, 2.5 mg/kg, 2.4 mg/kg, 2.3 mg/kg, 2.2 mg/kg, 2.1 mg/kg, 2.0 mg/kg, 1.9 mg/kg, 1.8 mg/kg, 1.7 mg/kg, 1.6 mg/kg, 1.5 mg/kg, 1.4 mg/kg, 1.3 mg/kg, 1.2 mg/kg, 1.1 mg/kg, 1.0 mg/kg, 0.9 mg/kg, 0.8 mg/kg, 0.7 mg/kg, or 0.6 mg/kg.

[00217] In some embodiments, the amount of the antibody (e.g., JSP191) or antigen binding fragment thereof administered is 0.5 mg/kg to 4.5 mg/kg, 0.5 mg/kg to 4 mg/kg, 0.5 mg/kg to 3.5 mg/kg, 0.5 mg/kg to 3 mg/kg, 0.5 mg/kg to 2.5 mg/kg, 1.5 mg/kg to 2.5 mg/kg, 1.8 mg/kg to 2.2 mg/kg, 1 mg/kg to 2 mg/kg, 1.2 mg/kg to 1.8 mg/kg, 1.3 mg/kg to 1.7 mg/kg, 1.4 mg/kg to 1.6 mg/kg, 0.5 mg/kg to 1.5 mg/kg, 0.7 mg/kg to 1.3 mg/kg, 0.8 mg/kg to 1.2 mg/kg, or 0.9 mg/kg to 1.1 mg/kg.

[00218] In one embodiment, the amount of the antibody (e.g., JSP191) or antigen binding fragment thereof administered is 35 mg to 350 mg. In some embodiments, the amount administered is at least 35 mg, 42 mg, 49 mg, 56 mg, 63 mg, 70 mg, 77 mg, 84 mg, 91 mg, 98 mg, 105 mg, 112 mg, 119 mg, 126 mg, 133 mg, 140 mg, 147 mg, 154 mg, 161 mg, 168 mg, 175 mg, 182 mg, 189 mg, 196 mg, 203 mg, 210 mg, 245 mg, 280 mg, or 315 mg.

[00219] In some embodiments, the amount administered is not greater than 350 mg, 315 mg, 280 mg, 245 mg, 210 mg, 203 mg, 196 mg, 189 mg, 182 mg, 175 mg, 168 mg, 161 mg, 154 mg, 147 mg, 140 mg, 133 mg, 126 mg, 119 mg, 112 mg, 105 mg, 98 mg, 91 mg, 84 mg, 77 mg, 70 mg, 63 mg, 56 mg, 49 mg, or 42 mg.

[00220] In some embodiments, the amount of the antibody (e.g., JSP191) or antigen binding fragment thereof administered is 35 mg to 315 mg, 35 mg to 280 mg, 35 mg to 245 mg, 35 mg to 210 mg, 35 mg to 175 mg, 105 mg to 175 mg, 126 mg to 156 mg, 70 mg to 140 mg, 98 mg to 126 mg, 91 mg to 109 mg, 98 mg to 112 mg, 35 mg to 105 mg, 49 mg to 91 mg, 56 mg to 84 mg, or 63 mg to 77 mg.

[00221] In one embodiment, the administration is once every 2-24 weeks. In one embodiment, the administration is once every 3-18 weeks. In one embodiment, the administration is once every 3-15 weeks. In one embodiment, the administration is once every 2-12 weeks. In one embodiment, the administration is once every 4-15 weeks. In one embodiment, the administration is once every 4-12 weeks. In one embodiment, the administration is once every 4-8 weeks. In one embodiment, the administration is once every 5-7 weeks. In one embodiment, the administration is once every 2-12 weeks. In some embodiments, the administration is no more than once every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 6 weeks, every 7 weeks, every 8 weeks, every 9 weeks, every 10 weeks, or every 11 weeks. In some embodiments, the administration is at least once every 12 weeks, every 11 weeks, every 10 weeks, every 9 weeks, every 8 weeks, every 7 weeks, every 6 weeks, every 5 weeks, every 4 weeks, or every 3 weeks.

[00222] In some embodiments, the administration is subcutaneous. In some embodiments, the administration is intravenous injection. In some embodiments, the administration is intramuscular injection.

[00223] In some embodiments, a first dose of the administration results in mast cell count reduction in the subject for at least 1 week, 2 weeks, 3 weeks, or 4 weeks.

[00224] In one embodiment, the present disclosure provides a method for treating, inhibiting, or preventing a mast cell-mediated disease or disorder in a subject in need thereof by administering to the subject an effective amount of an anti-CD117 antibody (e.g., JSP191) or fragment thereof of the present disclosure at a dose of 0.5 mg/kg to 5 mg/kg once every 2-12 weeks.

[00225] In another embodiment, provided a method for treating, inhibiting, or preventing a mast cell-mediated disease or disorder in a subject in need thereof by administering to the subject an effective amount of an anti-CD117 (e.g., JSP191) antibody or fragment thereof of the present disclosure at a dose of 1 mg/kg to 2 mg/kg once every 3-10 weeks.

[00226] In another embodiment, provided a method for treating, inhibiting, or preventing a mast cell-mediated disease or disorder in a subject in need thereof by administering to the subject an effective amount of an anti-CD117 antibody (e.g., JSP191) or fragment thereof of the present disclosure at a dose of 1.2 mg/kg to 1.8 mg/kg once every 4-8 weeks.

[00227] In one embodiment, the present disclosure provides a method for treating, inhibiting, or preventing a mast cell-mediated disease or disorder in a subject in need thereof by administering to the subject an effective amount of an anti-CD117 antibody (e.g., JSP191) or fragment thereof of the present disclosure at a dose of 35 mg to 350 mg once every 2-12 weeks.

[00228] In another embodiment, provided a method for treating, inhibiting, or preventing a mast cell-mediated disease or disorder in a subject in need thereof by administering to the subject an effective amount of an anti-CD117 antibody (e.g., JSP191) or fragment thereof of the present disclosure at a dose of 70 mg to 140 mg once every 3-10 weeks.

[00229] In another embodiment, provided a method for treating, inhibiting, or preventing a mast cell-mediated disease or disorder in a subject in need thereof by administering to the subject an effective amount of an anti-CD117 (e.g., JSP191) antibody or fragment thereof of the present disclosure at a dose of 84 mg to 126 mg once every 4-8 weeks.

[00230] In particular embodiments, treatment results in improvement in one or more symptoms of the disease or disorder. In particular embodiments, e.g., for the treatment of CSU or CInU, treatment results in an improvement in the subject's UAS7 score following treatment. In certain embodiments, the UAS7 score is reduced by at least 10%, at least 20%, at least 30%, at least

40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or by 100% as compared to the subject's UAS7 score prior to treatment or at the time of first dose. In some embodiments, the subject's UAS7 score following treatment is less than or equal to 4, less than or equal to 5, less than or equal to 6, less than or equal to 7, or less than or equal to 8. In some embodiments, the subject's UAS7 score following treatment is less than or equal to 6. In some embodiments, the subject's UCT score following treatment is greater than or equal to 10, greater than or equal to 11, greater than or equal to 12, greater than or equal to 13, or greater than or equal to 14. In some embodiments, the subject's UCT score following treatment is greater than or equal to 12. In some embodiments, the UAS7 scores and/or UCT are determined prior to treatment or at the time of first dose administration and then again at about 4, 6, 8, 12, 16, or 24 weeks following administration of the first dose. In some embodiments, the UAS7 scores and/or UCT are determined prior to treatment or at the time of first dose administration and then again at about 12 weeks following administration of the first dose.

[00231] In certain embodiments, the disclosure provides a method of treating, inhibiting, or preventing CSU in a mammalian subject, e.g., a human, comprising administering to the subject an effective amount of an anti-c-Kit antibody, e.g., briquilimab, wherein the anti-c-Kit antibody is administered subcutaneously at a dose of about 50 mg to about 300 mg or about 0.5 mg/kg to about 5 mg/kg. In certain embodiments, the subject is administered one or more doses of the anti-c-Kit antibody.

[00232] In certain embodiments, the disclosure provides a method of treating, inhibiting, or preventing an anaphylactoid reaction in a mammalian subject, e.g., a human, comprising administering to the subject an effective amount of an anti-c-Kit antibody, e.g., briquilimab, wherein the anti-c-Kit antibody is administered subcutaneously or intravenously at a dose of about 50 mg to about 300 mg or about 0.5 mg/kg to about 5 mg/kg. In certain embodiments, the subject is administered one or more doses of the anti-c-Kit antibody. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, is administered as one or more doses of about 0.2 to about 3.0 mg/kg patient weight or about 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 40 mg to about 200 mg, e.g., about 80 mg, about 90 mg/kg, about 100 mg, about 110 mg, or about 120 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody, e.g., JSP191, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, is administered subcutaneously.

[00233] In certain embodiments, the disclosure provides a method of treating, inhibiting, or preventing an allergic reaction in a mammalian subject, e.g., a human, comprising administering to the subject an effective amount of an anti-c-Kit antibody, e.g., briquilimab, wherein the anti-c-Kit antibody is administered subcutaneously or intravenously at a dose of about 50 mg to about 300 mg or about 0.5 mg/kg to about 5 mg/kg. In certain embodiments, the subject is administered one or more doses of the anti-c-Kit antibody. In particular embodiments, the allergic reaction is a severe allergic reaction. In particular embodiments, the allergic reaction is allergen-induced atopic dermatitis. In particular embodiments, the allergic reaction is a severe allergic reaction. In certain embodiments, the allergic reaction is allergen-induced asthma.

Hematopoietic Stem/Progenitor Cell Diseases and Disorders

[00234] Hematopoietic stem and progenitor cells (HSPCs) play a crucial role in the development and maintenance of the blood and immune system. They are capable of differentiating into various types of blood cells, including red blood cells, white blood cells, and platelets. Due to their regenerative and immunological properties, HSPCs have been extensively studied in the context of various diseases. CD117 is highly expressed on HSPCs, particularly on multipotent progenitor cells and early hematopoietic stem cells (HSCs). CD117 expression is also found on certain cancer cells, including acute myeloid leukemia (AML).

[00235] Accordingly, there is a need in the art for compositions and methods for depleting mast cells and/or hematopoietic stem and progenitor cells (HSPCs), and for treating mast cell diseases and disorders and HSPC diseases and disorders.

[00236] Compositions and methods disclosed herein may be used to treat hematopoietic stem/progenitor cell disease and disorders, including but not limited to malignancies.

[00237] CD117, also known as c-kit or stem cell factor receptor, plays an important role in hematopoietic stem cells (HSCs), which are responsible for generating the different types of blood cells, and HSPCs. HSC maintenance and self-renewal: CD117 plays a role in maintaining the pool of HSCs and promoting their self-renewal capacity. Binding of stem cell factor (SCF) to CD117 activates signaling pathways that support HSC survival, prevent their differentiation, and promote their ability to divide and generate new HSCs. CD117 downregulation is required for the differentiation of HSCs into various blood cell lineages. Normally, the regulation of CD117 expression is tightly controlled to ensure the proper balance between self-renewal and differentiation of HSCs. CD117 signaling is involved in the mobilization of HSCs from the bone marrow into the peripheral blood. The interaction between CD117-expressing HSCs and

the bone marrow microenvironment, also known as the stem cell niche, is important for HSC maintenance and regulation. The expression of CD117 on HSCs allows them to respond to SCF, which is produced by various cells in the bone marrow microenvironment. SCF binding to CD117 promotes the interaction between HSCs and their niche, providing essential signals for HSC survival, quiescence, and regulation.

[00238] In certain embodiments, methods disclosed herein are used to modulate one or more HSC or HSPC activities, e.g., to inhibit HSPC maintenance, inhibiting HSPC self-renewal, promote HSPC differentiation, inhibit HSPC mobilization, or inhibit HSPC interaction with the bone marrow microenvironment.

[00239] In certain embodiments, the disclosure provides a method of depleting HSPCs in a subject, comprising administering to the subject an anti-c-kit antibody, e.g., JSP191, or an antigen-binding fragment thereof, e.g., a (Fab')₂, e.g., a JSP191 (Fab')₂, wherein the method results in decrease in the amount of HSPCs in a subject, e.g., immediately following the administration of the antibody or antigen-binding fragment thereof, or at about one day, two days, three days, four days, five days, six days, ten days, one week, two weeks, one month, two months, four months, or six months following administration of the antibody or antigen-binding fragment thereof. In certain embodiments, the method results in decrease in the amount of HSPCs in a subject, e.g., immediately following the conclusion of treatment, or at about one day, two days, three days, four days, five days, six days, ten days, one week, two weeks, one month, two months, four months, or six months following the conclusion of treatment. In particular embodiments, the HSPCs are diseased HSPCs. In some embodiments, the methods described herein deplete diseased HSPCs from a subject by administering an anti-c-kit antibody or fragment thereof, e.g., (Fab')₂ fragment, to the subject. In some embodiments, diseased HSPCs are depleted from the subject, or a tissue or organ of the subject, by at least or about 2%, at least or about 5%, at least or about 10%, at least or about 20%, at least or about 30%, at least or about 40%, at least or about 50%, at least or about 60%, at least or about 70%, at least or about 80%, at least or about 90%, at least or about 95%, at least or about 98%, at least or about 99%, or at least or about 100% of total diseased HSPCs in the subject. In certain embodiments, the treatments completely or almost completely deplete diseased HSPCs from the subject.

[00240] In some embodiments, the treatments described herein selectively deplete diseased HSPCs in a subject. In particular embodiments, selective depletion of diseased HSPCs according to a disclosed method results in the depletion of a greater number or percentage of diseased HSPCs as compared to the number or percentage of non-diseased HSPCs that are

depleted. In particular embodiments, the methods deplete diseased HSPCs and/or induce diseased HSPC apoptosis. In certain embodiments, the method depletes at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or all of the subject's diseased HSPCs, or induces apoptosis of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or all of the subject's diseased HSPCs, at about two weeks following administration of the antigen-binding fragment. In certain embodiments the subject's HSPCs or diseased HSPCs are depleted by about 5% or less, about 10% or less, or about 20% or less at about 3-4 months following administration of the antigen-binding fragment.

[00241] In particular embodiments, the anti-c-kit antibody or fragment thereof, e.g., (Fab')₂ fragment, is provided to the subject in a dose effective to deplete diseased HSPCs cells in a subject being treated. In certain embodiments, the methods induce apoptosis of the HSPCs. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191, or fragment thereof, is administered as one or more doses of about 0.1 mg/kg to about 2.0 mg/kg, 0.2 mg/kg to about 3.0 mg/kg patient weight, about 0.3 mg/kg to about 1.5 mg/kg, 0.5 mg/kg to about 2.0 mg/kg, e.g., about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, 0.8 mg/kg, or 1.0 mg/kg, or 2.0 mg/kg, or about 30 mg/kg to about 150 mg/kg, about 40 mg/kg to about 200 mg/kg, e.g., about 60 mg/kg, about 70 mg/kg, about 80 mg, about 90 mg/kg, or about 100 mg. In certain embodiments, the patients are treated with the monoclonal anti-c-kit IgG antibody or fragment thereof, e.g., a JSP191 (Fab')₂ fragment, about once every eight weeks to about six months, e.g., about once every eight weeks to about 12 weeks, e.g., about once every eight weeks, about once every 12 weeks, about once every four months, or about once every six months. In particular embodiments, the anti-c-Kit antibody, e.g., JSP191 is administered intravenously or subcutaneously. In certain embodiments, the subject's bone marrow comprises at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 15%, or at least 20% healthy HSCs prior to treatment.

[00242] In related embodiments, the disclosure provides a method of treating a hematopoietic stem/progenitor cell (HSPC) disease or disorder in a human subject, the method comprising administering to the subject an anti-c-kit antibody or an antigen-binding fragment thereof, optionally wherein the antigen-binding fragment is a F(ab')₂. In certain embodiments, the subject's HSPCs are depleted by at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% at about 7-15 days following administration of the antibody or antigen-binding fragment thereof.

[00243] In particular embodiments, the method is used to treat a disease or disorder selected from the group consisting of: myelodysplastic syndromes, leukemias, optionally acute myeloid leukemia (AML), and clonal hematopoiesis of indeterminate potential (CHIP).

[00244] Myelodysplastic syndrome (MDS) is a hematologic malignancy characterized by the presence of defective hematopoietic stem cells (HSC). Current treatments for MDS include hematopoietic stimulating agents for temporary resolution of associated symptoms. These may include chronic transfusions, erythropoietin stimulating agents for red blood production, or various chemotherapies. However, there are no existing treatments that specifically target diseased HSC relative to healthy HSC. Therefore, there is a need for innovative agents and regimens that selectively target diseased HSC and permit healthy HSC to undergo normal hematopoiesis in the bone marrow. The present disclosure meets this need by providing agents and regimens for selective depletion of diseased HSC in MDS, acute myeloid leukemia (AML), and other disorders.

[00245] Leukemias are a group of cancers that affect the blood and bone marrow, where blood cells are produced. They arise from abnormal growth and proliferation of immature blood cells, e.g., hematopoietic stem/progenitor cells. Leukemias can be classified into four main types based on their progression and the types of blood cells affected: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).

[00246] ALL is the most common type of leukemia in children, although it can also affect adults. ALL originates from abnormal lymphocyte precursors, which are a type of white blood cell involved in the immune response. The disease progresses rapidly, with immature lymphoblasts crowding out normal cells in the bone marrow and interfering with their function.

[00247] AML typically affects adults, but it can also occur in children. It develops from abnormal myeloid cells, which give rise to various types of mature blood cells, including red blood cells, platelets, and certain types of white blood cells. In AML, immature myeloid cells accumulate in the bone marrow and bloodstream, disrupting normal blood cell production.

[00248] CLL is primarily seen in older adults and is characterized by the accumulation of abnormal, mature lymphocytes. These cells, which are derived from B lymphocytes, gradually replace normal white blood cells in the bone marrow and circulate in the blood. CLL often progresses slowly and may not cause symptoms in the early stages.

[00249] CML usually affects adults and is characterized by the overproduction of granulocytes, a type of white blood cell. It is associated with a specific genetic abnormality called the Philadelphia chromosome, which results in the formation of an abnormal fusion

protein called BCR-ABL. CML progresses slowly through three phases: chronic phase, accelerated phase, and blast crisis.

[00250] CHIP is a disorder characterized by the presence of a population of genetically distinct blood cells in an individual's bone marrow and peripheral blood. In CHIP, a specific mutation occurs in the DNA of hematopoietic stem cells, which results in the presence of a clone of abnormal cells alongside the normal cells in the blood. The specific mutation commonly associated with CHIP is in genes such as DNMT3A, TET2, and ASXL1, although other mutations can also occur. CHIP does not cause any obvious symptoms or clinical manifestations, and people with CHIP generally have normal blood cell counts and do not experience any signs of bone marrow dysfunction or blood-related symptoms. However, CHIP is associated with an increased risk of developing certain hematologic malignancies, such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). The presence of the mutation in CHIP confers a higher likelihood of progression to these diseases over time. The risk of progression varies depending on the specific genetic mutation and other factors.

Anti-c-Kit Antibodies

[00251] Methods disclosed herein contemplate the use of an anti-c-kit antibody. In some embodiments, the disclosure provides methods for selectively depleting endogenous mast cells and/or diseased hematopoietic stem cells (HSCs) in a subject by administering an anti-c-kit antibody or antigen-binding fragment thereof, e.g., a (Fab')₂ fragment. In some embodiments, the compositions and methods disclosed herein may be applicable to any anti-c-kit antibody that blocks stem cell factor (SCF) binding to a c-kit/CD117 protein of an endogenous HSC. In some embodiments the antibody is a monoclonal anti-human c-kit antibody. In some embodiments, the antibody is an antigen-binding fragment of an antibody that blocks stem cell factor (SCF) binding.

[00252] In particular embodiments, methods disclosed herein are practiced using an (Fab')₂ fragment, e.g., a JSP191 (Fab')₂ antibody fragment. The (Fab')₂ fragment refers to a specific antibody fragment that is generated by enzymatic cleavage of the intact antibody molecule with pepsin. Pepsin cleaves the antibody just below or within the hinge region. The (Fab')₂ fragment includes two Fab joined together through disulfide bonds, so they are divalent with a molecular weight of about 110 kDa, as compared to about 150 kDa for a whole IgG antibody. The (Fab')₂ contains the variable regions of both the heavy and light chains, which contribute to the specificity of the antibody. Thus, the (Fab')₂ fragment retains the antigen-binding capabilities

of the intact antibody but lacks the Fc region. (Fab')₂ fragments may be produced by digestion of a full IgG antibody with pepsin or other enzymes, such as digestion at a single site below the hinge of IgG using the site-specific cysteine protease FabRICATOR (IdeS)(Genovis Inc., USA). (Fab')₂ may also be produced recombinantly, e.g., by expressing full antibody light chains and truncated antibody heavy chains that lack the Fc region but include the variable region and some or all of the hinge region. For additional methods of producing (Fab')₂, see, e.g., Rosenstein, s. et al., Curr Protoc Mol Biol. 2020 Jun; 131(1):e119.

[00253] A number of antibodies and fragments thereof, including (Fab')₂, contemplated by the disclosure that specifically bind human CD117 are known in the art and/or commercially available, including without limitation JSP-191, SR1, 2B8, ACK2, YB5-B8, 57A5, and 104D2. In certain embodiments, the anti-c-kit antibody is selected from the group consisting of: JSP191 (Jasper Therapeutics; Redwood City, CA); CDX-0158 (formerly KTN0158) or CDX-0159 (Celldex Therapeutics, Hampton, NJ); MGTA-117 (AB85) (Magenta Therapeutics, Cambridge, MA); CK6 (Magenta Therapeutics, Cambridge, MA); AB249 (Magenta Therapeutics, Cambridge, MA); and FSI-174 (Gilead, Foster City, CA). Antibodies from Magenta Therapeutics contemplated by the disclosure include but are not limited to those that are disclosed in US Patent Application Publication No. 20190153114, PCT Application Publication Nos. WO2019084064, WO2020/219748, and WO2020/219770. The FSI-174 antibody is disclosed in PCT application Publication No. WO2020/112687 and U.S. Patent Application Publication No. 20200165337. The disclosure includes but is not limited to any anti-c-kit antibodies and/or CDR sets disclosed in any of the patent application disclosed herein, which are all incorporated by reference in their entireties.

[00254] In certain embodiments, the anti-c-kit antibody binds to the extracellular region of CD117, i.e., amino acids 26-524. The sequence of this region is shown below:

QPSVSPGEPSPPSIHPGKSDLIVRVGDEIRLLCTDPGFVKWTFEILDETNNKQNEWIT
EKA EATNTGKYTCTNKHGLSNSIYVFVRDPAKLFLVDRSLYGKEDNDTLVRCPLTDP
EVTNYS LKGCQGKPLPKDLRFIPDPKAGIMIKSVKRAYHRLCLHCSVDQEGKSVLSE
KFILKVRPAFKA VPVSVSKASYLLREGEEFTVTCTIKDVSSSVYSTWKRENSQTKLQ
EKYNSWHHGDFNYERQATLTISSARVNDSGVFCYANNTFGSANVTITLEVVDKGF
INIFPMINTTVFVNDGENVDLIVEYEA FPKPEHQQWIYMNRTFTDKWEDYPKSENE
NIRYVSELHLTRLKGTEGGTYTFLVSNDSVNAAIAFN VYVNTKPEILTYDRLVNGML
QCVAAGFPEPTIDWYFCPGTEQRCSASVLPVDVQTLNSSGPPFGKLVVQSSIDSSAFK
HNGTVECKAYNDVGKTSAYFNFAFKGNNKEQIHPHTLFTP (SEQ ID NO: 1).

[00255] Illustrative anti-c-kit antibodies include, but are not limited to, SR-1, JSP191, 8D7, K45, 104D2, CK6, YB5.B8, AF-2-1, AF11, AF12, AF112, AF-3, AF-1-1, NF, NF-2-1, NF11, NF12, NF112, NF-3, HF11, HF12, and HF112. A number of antibodies contemplated by the disclosure that specifically bind human CD117 are commercially available, including without limitation SR1, 2B8, ACK2, YB5-B8, 57A5, 104D2, etc. In certain embodiments, the anti-c-kit antibody is selected from the group consisting of: JSP191, CDX-0159 (from Celldex Therapeutics, Hampton, NJ), MGTA-117 (AB85) (from Magenta Therapeutics, Cambridge, MA), CK6 (from Magenta Therapeutics, Cambridge, MA), AB249 (from Magenta Therapeutics, Cambridge, MA), and FSI-174 (from Gilead, South San Francisco, CA). The antibodies from Magenta Therapeutics are disclosed in US Patent Application Publication No. 20190153114. In certain embodiments, the antibody is one disclosed in any of US Pat. Nos. 7,915,391, US 8,436,150, or US 8,791,249. In certain embodiments, the antibody is one disclosed in US Pat. Application Publ. No 20200165337 or any of PCT Publication Nos. WO 2020/112687, WO2020/219748, WO 2020/219770, or WO 2019/084064.

[00256] In particular embodiments, the antibody is a humanized form of SR1, a murine anti-c-kit antibody described in U.S. Pat. Nos. 5,919,911 and 5,489,516. The humanized form, referred to as JSP191 or briquilimab, is disclosed in U.S. Patent Nos. 7,915,391, 8,436,150, and 8,791,249. JSP191 is an aglycosylated IgG1 humanized antibody with the N-linked glycosylation site removed from the IgG1 constant region. JSP191 specifically binds to human CD117, a receptor for stem cell factor (SCF), which is expressed on the surface of a variety of cell types, including mast cells, hematopoietic stem and progenitor cells, melanocytes, germ cells, and interstitial cells of Cajal. JSP191 blocks SCF from binding to CD117 and disrupts stem cell factor (SCF) signaling. JSP191 binding to c-Kit inhibits the binding of the ligand stem cell factor (SCF). In cultured mast cells, JSP191 can inhibit IgE-mediated mast cell degranulation. In a human mast cell survival bioassay, JSP191 has an IC₅₀ of about 12.5 nM. In mast cells, activated KIT potentiates degranulation and regulates MC growth, differentiation, survival and chemotaxis (Gilfillan, Austin, and Metcalfe 2011). Inhibition of SCF signaling through c-Kit on mast cells leads to their apoptosis. JSP191 has a half life of about 9 days. PK clearance of JSP191 allows for restoration of c-Kit signaling on other c-Kit expressing cells once mast cells are depleted. Following depletion, tissue mast cells likely take more than 8 weeks to be replenished through differentiation from hematopoietic stem cells.

[00257] JSP191 (briquilimab) is a heterotetramer consisting of 2 heavy chains of the IgG1 subclass and 2 light chains of the kappa subclass, which are covalently linked through disulfide bonds. There are no N-linked glycans on JSP191 due to an intentional substitution from an

asparagine to glutamine at heavy chain residue 297. The sequences of the heavy chains and light chains of JSP191 are disclosed as SEQ ID NO: 4 from US8436150 and SEQ ID NO: 2 from US8436150, respectively.

[00258] The sequences of the heavy chains and light chains of JSP191 are disclosed as SEQ ID NO: 4 from U.S. Patent No. 8,436,150 and SEQ ID NO: 2 from U.S. Patent No. 8,436,150, respectively. The sequences of the heavy and light chains of JSP191 are:

Heavy Chain:

MDWTWRVFCLLAVAPGAHSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMH
WVRQAPGQGLEWMGVIYSGNGDTSYNQKFKGRVTITADKSTSTAYMELSSLRSED
AVYYCARERDTRFGNWGQGLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVV
VDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO: 2)

and

Light Chain:

MVLQTQVFISLLLWISGAYGDIVMTQSPDSLAVSLGERATINCRASESVDIYGNSFMH
WYQQKPGQPPKLLIYLASNLESQVDFRSGSGSGTDFTLTISSLQAEDVAVYYCQQN
NEDPYTFGGGKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSP
TKSFNRGEC (SEQ ID NO: 3).

[00259] In certain embodiments, the variable heavy domain of JSP191 comprises the following sequence:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQAPGQGLEWMGVIYSG
NGDTSYNQKFKGRVTITADKSTSTAYMELSSLRSEDVAVYYCARERDTRFGNWGQ
GLTVSS (SEQ ID NO: 4).

[00260] In certain embodiments, the variable light chain domain of JSP191 comprises the following sequence:

DIVMTQSPDSLAVSLGERATINCRASESVDIYGNSFMHWYQQKPGQPPKLLIYLASN
LESQVDFRSGSGSGTDFTLTISSLQAEDVAVYYCQQNNEP YTFGGGKVEIK (SEQ
ID NO: 5).

[00261] The CDRs present in JSP191 are as follows: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); VH CDR3 = ERDTRFGN (SEQ ID NO: 8); VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEP (SEQ ID NO: 11).

[00262] CDX-0159 is a humanized monoclonal antibody that specifically binds the receptor tyrosine kinase KIT with high specificity and potentially inhibits its activity. CDX-0159 is designed to block KIT activation by disrupting both SCF binding and KIT dimerization. CDX-0159 and other anti-c-kit antibodies are described in U.S. Patent No. 10,781,267, and in particular embodiments, an anti-c-kit disclosed herein comprises the CDRs of any of the antibodies disclosed therein. In certain embodiments, the anti-c-kit antibody comprises: (i) a light chain variable region ("VL") comprising the amino acid sequence:

DIVMTQSPSX_{K1}LSASVGDRVTITCKASQNVRTNVAWYQQKPGKAPKX_{K2}LIYSASYR
YSGVPDRFX_{K3}GSGSGTDFTLTISSLQX_{K4}EDFAX_{K5}YX_{K6}CQQYNSYPRTFGGGTKVEIK
(SEQ ID NO: 12), wherein X_{K1} is an amino acid with an aromatic or aliphatic hydroxyl side chain, X_{K2} is an amino acid with an aliphatic or aliphatic hydroxyl side chain, X_{K3} is an amino acid with an aliphatic hydroxyl side chain, X_{K4} is an amino acid with an aliphatic hydroxyl side chain or is P, X_{K5} is an amino acid with a charged or acidic side chain, and X_{K6} is an amino acid with an aromatic side chain; and (ii) a heavy chain variable region ("VH") comprising the amino acid sequence:

QVQLVQSGAEX_{H1}KKPGASVKX_{H2}SCKASGYTFTDYYINAVVX_{H3}QAPGKGLEWIARI
YPGSGNTYYNEKFKGRX_{H4}TX_{H5}TAX_{H6}KSTSTAYMX_{H7}LSSLRSEDX_{H8}AVYFCARGV
YYFDYWGGQTTVTVSS (SEQ ID NO: 13), wherein X_{H1} is an amino acid with an aliphatic side chain, X_{H2} is an amino acid with an aliphatic side chain, X_{H3} is an amino acid with a polar or basic side chain, X_{H4} is an amino acid with an aliphatic side chain, X_{H5} is an amino acid with an aliphatic side chain, X_{H6} is an amino acid with an acidic side chain, X_{H7} is an amino acid with an acidic or amide derivative side chain, and X_{H8} is an amino acid with an aliphatic hydroxyl side chain. In specific aspects, described herein are antibodies (*e.g.*, human or humanized antibodies), including antigen-binding fragments thereof, comprising: (i) VH CDRs of a VH domain comprising the amino acid sequence:

QVQLKQSGAELVRPGASVKLSCKASGYTFTDYYINWVKQRPQGQGLEWIARIYPG
SGNTYYNEKFKGKATLTAEKSSSTAYMQLSSLTSEDSAVYFCARGVYYFDYWGG
GTTLTVSS (SEQ ID NO: 14) or

QVQLKQSGAELVRPGASVKLSCKASGYTFTDYYINWVKQRPQGQGLEWIARIYPG
SGNTYYNEKFKGKATLTAEKSSSTAYMQLSSLTSEDSAVYFCARGVYYFDYWGG
GTTLTVSA (SEQ ID NO: 15), and

(ii) VL CDRs of a VL domain comprising the amino acid sequence:

DIVMTQSQKFMSTSVGDRVSVTCKASQNVRTNVAWYQQKPGQSPKALIYSASYRYS
GVPDRFTGSGSGTDFTLTI SNVQSEDLADYFCQQYNSYPRTFGGGTKLEIKR (SEQ ID
NO: 16).

[00263] MGTA-117 (AB85) is a CD117-targeted antibody engineered for the transplant setting and conjugated to amanitin, which is being developed for patients undergoing immune reset through either autologous or allogeneic stem cell transplant. MGTA-117 depletes hematopoietic stem and progenitor cells, and this antibody and others contemplated by the disclosure are described in U.S. Application Publication No. 20200407440 and/or PCT Application Publication No. WO2019084064. Epitope analysis of AB85 binding to CD177 is described in PCT Application Publication No. WO2020219770, which identified the following two epitopes within CD117:

EKAETNTGKYTCTNKHGLSNSIYVFVRDPA (SEQ ID NO: 17; amino acids 60-90), and
RCPLTDPEVTNYSKGCQGKP (SEQ ID NO: 18; amino acids 100-130).

[00264] The sequences of the variable heavy chain and variable light chains of AB85 are disclosed as SEQ ID NO: 143 and SEQ ID NO: 144 from PCT Application Publication No. WO2019084064, respectively.

[00265] The heavy chain variable region (VH) amino acid sequence of Ab85 is:

EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYWIGWVRQMPGKGLEWMAIINPRDS
DTRYRPSFQGQVTISADKSISTAYLQWSSLKASDTAMYVCARHGRGYEGYEGAFDI
WGQGTLLTVSS (SEQ ID NO: 19).

[00266] The VH CDR amino acid sequences of AB85 are as follows: NYWIG (SEQ ID NO: 20; VH CDR1); IINPRDS DTRYRPSFQG (SEQ ID NO: 21; VH CDR2); and HGRGYEGYEGAFDI (SEQ ID NO: 22; VH CDR3).

[00267] The light chain variable region (VL) amino acid sequence of AB85 is:

DIQMTQSPSSLSASVGDRVTITCRSSQGIRSDLGWYQQKPGKAPKLLIYDASNLETGV
PSRFGSGSGTDFLTISLQPEDFATYYCQQANGFPLTFGGGTKVEIK (SEQ ID NO:
23).

[00268] The VL CDR amino acid sequences of AB85 are as follows: RSSQGIRSDLG (SEQ ID NO: 24; VL CDR1); DASNLET (SEQ ID NO: 25; VL CDR2); and QQANGFPLT (SEQ ID NO: 26; VL CDR3).

[00269] FSI-174 is an anti-cKIT antibody being developed in combination with 5F9 as a non-toxic transplant conditioning regimen, as well as a treatment for targeted hematologic malignancies. The sequences of FSI-174 are disclosed in PCT Application Publication No. 2020/112687, U.S. Patent Application Publication No. 20200165337, and U.S. Patent No.

11,041,022. In particular embodiments, an anti-c-kit antibody comprises the three CDRs or variable heavy chain regions present in any of AH1, AH2, AH3, AH4, or AH5 disclosed therein, and/or the three CDRs or variable heavy chain regions present in any of AL1 or AL2 disclosed therein.

[00270] In certain embodiments, the CDRs present in FSI-174 and related antibodies are as follows: VH CDR1 = SYNMH (SEQ ID NO: 27); VH CDR2 = VIYSGNGDTSY(A/N)QKF(K/Q)G (SEQ ID NO: 28); VH CDR3 = ERDTRFGN (SEQ ID NO: 29); VL CDR1 = RAS(D/E)SVDIYG(N/Q)SFMH (SEQ ID NO: 30); VL CDR2 = LASNLES (SEQ ID NO: 31); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 32). A/N and the like indicate that the amino acid position may be either of the two amino acids, in this example, A or N. In certain embodiments, CDRs present in the heavy variable region are CDRs H1, H2 and H3 as defined by Kabat: H1 = SYNMH (SEQ ID NO: 27); H2 = VIYSGNGDTSYAQKFKG (SEQ ID NO: 33); H3 = ERDTRFGN (SEQ ID NO: 29); and the CDRs present in the light variable region are CDRs L1, L2 and L3 as defined by Kabat: L1 = RASESVDIYGQSFMH (SEQ ID NO: 34); L2 = LASNLES (SEQ ID NO: 31); and L3 = QQNNEDPYT (SEQ ID NO: 32), respectively except that 1, 2, or 3 CDR residue substitutions is/are present selected from N to A at heavy chain position 60, K to Q at heavy chain position 64 and N to Q at light chain position 30, positions being numbered according to Kabat. In certain embodiments, the antibody comprises any of the heavy chain variable region sequences (AH2, AH3, AH4) and/or light chain variable chain region sequences provided below (AL2), or the CDRs therein shown underlined:

AH2:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMNHWVRQAPGQGLEWMGVIYSG
NGDTSYAQKFKGRVTITADKSTSTAYMELSSLRSEDVAVYYCARERDTRFGNWGQG
TLVTVSS (SEQ ID NO: 35)

AH3:

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMNHWVRQAPGQGLEWMGVIYSG
NGDTSYNQKFQGRVTITADKSTSTAYMELSSLRSEDVAVYYCARERDTRFGNWGQG
TLVTVSS (SEQ ID NO: 36)

AH4

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYMNHWVRQAPGQGLEWMGVIYSG
NGDTSYAQKFQGRVTITADKSTSTAYMELSSLRSEDVAVYYCARERDTRFGNWGQG
TLVTVSS (SEQ ID NO: 37)

AL2:

DIVMTQSPLSLPVTPGEPASISCRASESVDIYGQSFMHYQQKPGQPPKLLIYLASNL
ESGVPDRFSGSGGTDFTLKISRVEAEDVGVYYCQQNNEDPYTFGGGTKVEIK (SEQ
ID NO: 38).

[00271] In certain embodiments, the anti-c-kit antibody comprises the full heavy chain and/or full light chain of any of the antibodies disclosed herein, or an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 98%, at least 99% identity to a heavy or light chain disclosed herein, *e.g.*, a JSP191 heavy or light chain. In certain embodiments, the anti-c-kit antibody comprises the variable region of a heavy chain and/or light chain of any of the antibodies disclosed herein, or an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 98%, at least 99% identity to the variable region of a heavy or light chain disclosed herein, *e.g.*, a JSP191 heavy or light chain variable region. In certain embodiments, the anti-c-kit antibody comprises a heavy chain and/or a light chain comprising one or more CDRs of an antibody disclosed herein, *e.g.*, two, three, four, five or six CDRs of an antibody disclosed herein, *e.g.*, a JSP191 antibody. In particular embodiments, the anti-c-kit antibody comprises a heavy chain or variable region thereof comprising one, two, or three heavy chain CDRs disclosed herein, *e.g.*, a JSP191 heavy chain. In particular embodiments, the anti-c-kit antibody comprises a light chain or variable region thereof comprising one, two, or three light chain CDRs disclosed herein, *e.g.*, a JSP191 light chain.

[00272] CDX-0159 is a humanized monoclonal antibody that specifically binds the receptor tyrosine kinase KIT with high specificity and potently inhibits its activity. CDX-0159 is designed to block KIT activation by disrupting both SCF binding and KIT dimerization.

[00273] MGTA-117 is a CD117-targeted antibody engineered for the transplant setting and conjugated to amanitin, which is being developed for patients undergoing immune reset through either autologous or allogeneic stem cell transplant. MGTA-117 depletes hematopoietic stem and progenitor cells and this antibody and others contemplated by the disclosure are described in US 20200407440.

[00274] FSI-174 is an anti-c-kit antibody being developed in combination with 5F9 as a non-toxic transplant conditioning regimen, as well as a treatment for targeted hematologic malignancies.

[00275] In particular embodiments, the antibody may include one or more CDR with at least 70%, 80%, 90%, 95%, or 99% amino acid or nucleotide sequence identity to a CDR present in a humanized monoclonal antibody that binds c-kit, *e.g.*, an antibody derived from any of the mouse antibodies SR1, ACK2, ACK4, 2B8, 3C11, MR-1, and CD122. In some embodiments, the antibody blocks the binding of stem cell factor (SCF) to stem cell factor receptor (CD117). Illustrative embodiments of anti-c-kit antibodies that may be used include JSP191, as well as those described in WO2007127317A2 and US20200165337A1, both incorporated herein in their entirety.

[00276] In certain embodiments, the anti-c-kit antibody comprises the full heavy chain and/or full light chain of any of the antibodies disclosed herein, or an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 98%, at least 99% identity to a heavy or light chain disclosed herein, *e.g.*, a JSP191 heavy or light chain. In certain embodiments, the anti-c-kit antibody comprises the variable region of a heavy chain and/or light chain of any of the antibodies disclosed herein, or an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 98%, at least 99% identity to the variable region of a heavy or light chain disclosed herein, *e.g.*, a JSP191 heavy or light chain variable region. In certain embodiments, the anti-c-kit antibody comprises a heavy chain and/or a light chain comprising one or more CDRs of an antibody disclosed herein, *e.g.*, two, three, four, five or six CDRs of an antibody disclosed herein, *e.g.*, a JSP191 antibody. In particular embodiments, the anti-c-kit antibody comprises a heavy chain or variable region thereof comprising one, two, or three heavy chain CDRs disclosed herein, *e.g.*, a JSP191 heavy chain. In particular embodiments, the anti-c-kit antibody comprises a light chain or variable region thereof comprising one, two, or three light chain CDRs disclosed herein, *e.g.*, a JSP191 light chain.

Pharmaceutical Compositions, Unit Dosage Forms and Kits

[0277] In some embodiments, the anti-c-kit antibody or fragment thereof (or combination therapy) is present in a pharmaceutical composition. The present disclosure provides pharmaceutical compositions useful for the treatments disclosed herein. Such compositions comprise an effective amount of an antibody or fragment thereof, and an acceptable carrier. In some embodiments, the composition further includes a second therapeutic agent (*e.g.*, an antihistamine).

[0278] In particular embodiments, the pharmaceutical compositions may be in a water-soluble form, such as in pharmaceutically acceptable salts, which is meant to include both acid and base addition salts. Pharmaceutically acceptable acid addition salts include but are not limited to: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, and salicylic acid. Pharmaceutically acceptable base addition salts include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines,

substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

[0279] In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. Further, a "pharmaceutically acceptable carrier" will generally be a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Pharmaceutical compositions as described herein may also include one or more of the following: carrier proteins such as serum albumin; buffers; fillers such as microcrystalline cellulose, lactose, corn and other starches; binding agents; and polyethylene glycol.

[0280] The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents such as acetates, citrates or phosphates. Antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; and agents for the adjustment of tonicity such as sodium chloride or dextrose are also envisioned.

[0281] These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences by E. W. Martin, incorporated herein by reference.

[0282] Such compositions may contain a therapeutically effective amount of the antigen-binding polypeptide, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0283] In an embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous or subcutaneous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachet indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0284] The compounds of the disclosure can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0285] The compositions for administration will commonly include the antibody or fragment thereof dissolved in a pharmaceutically acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used, *e.g.*, buffered saline. The composition may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH and buffering agents, toxicity countering agents, *e.g.*, sodium acetate, sodium chloride, potassium chloride, calcium chloride, and sodium lactate. The concentration of active agents in the formulations can vary and are selected based on fluid volumes, viscosities, and body weight in accordance with the particular mode of administration selected and the patient's needs (*e.g.*, Remington's Pharmaceutical Science (15th ed., 1980) and Goodman & Gillman, The Pharmacological Basis of Therapeutics (Hardman et al., eds., 1996)).

[0286] The disclosure provides pharmaceutical compositions and unit dosage forms comprising an effective amount of an anti-c-kit antibody or antigen-binding fragment thereof.

[0287] The disclosure further provides kits comprising an anti-c-kit antibody or antigen-binding fragment thereof as described herein, e.g., a kit for administration of the anti-c-kit antibody or fragment thereof by a medical professional or the subject in need thereof. The kit may comprise for example, a container, and one or more doses of the anti-c-kit antibody, and instructions for use thereof. In certain embodiments, the kit comprises multiple doses of the anti-c-kit antibody or fragment thereof, suitable for a dosing regimen over a period of time. In certain embodiments, each dose comprises the same amount of the anti-c-kit antibody, while in other embodiments, the kit may comprises two or more different doses of the anti-c-kit antibody or fragment thereof. In certain embodiments, each dose is present within a separate container. In particular embodiments, each of the one or more doses comprises about 0.5 mg to about 800 mg of the anti-c-kit antibody or fragment thereof, optionally about 5 mg to about 800 mg of the anti-c-kit antibody. In particular embodiments, one or more doses comprises about 80 mg to about 280 mg, optionally about 80 mg, about 100 mg, about 120 mg, about 140 mg, about 160 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, or about 300 mg of the anti-c-kit antibody or fragment thereof. In particular embodiments, one or more doses comprises about 120 mg to about 240 mg, optionally about 120 mg, 180 mg, or about 240 mg, of the anti-c-kit antibody or fragment thereof.

[0288] In certain embodiments, the disclosure provides pharmaceutical compositions, unit dosage forms, and kits that comprise one or more doses of a monoclonal anti-c-kit IgG antibody or antigen binding fragment thereof, wherein each of the one or more doses comprises about 40 mg to about 360 mg, about 50 mg to about 600 mg, or about 50 mg to about 300 mg of the anti-c-kit antibody or fragment thereof, optionally wherein the anti-c-kit antibody is JSP191. In particular embodiments, each of the one or more doses comprises or consists of about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody. In certain embodiments, the kit comprises one or more doses, each independently comprising of about 40 mg, about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg or about 360 mg of the anti-c-kit

antibody or fragment thereof, optionally wherein the anti-c-kit antibody is JSP191. In particular embodiments, the kit comprises two or more doses of the anti-c-kit antibody. In certain embodiments, each of the two or more doses of the anti-c-kit antibody comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg of the anti-c-kit antibody, optionally wherein the anti-c-kit antibody is JSP191.

[0289] In another aspect, the disclosure provides pharmaceutical compositions, unit dosage forms, and kits comprising one or more doses of a monoclonal anti-c-kit IgG antibody, e.g., JSP191, wherein each of the one or more doses comprises about 40 mg to about 360 mg, about 50 mg to about 600 mg, about 50 mg to about 500 mg, about 50 mg to about 400 mg, about 50 mg to about 300 mg of the anti-c-kit antibody, optionally wherein the anti-c-kit antibody is JSP191. In some embodiments, each of the one or more doses comprises or consists of about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300, about 350 mg, about 360 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, or about 600 mg of the anti-c-kit antibody. In certain embodiments, the kit comprises one or more doses comprising of about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit antibody, optionally wherein the anti-c-kit antibody is JSP191.

[0290] In particular embodiments, the pharmaceutical compositions, unit dosage forms, and kits comprises a single, high dose in an amount sufficient to administer to the subject about 1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg of the anti-c-Kit antibody, e.g., JSP191. In some embodiments, the kit comprises two or more doses of the anti-c-kit antibody. In certain embodiments, each of the two or more doses of the anti-c-kit antibody comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 280 mg of the anti-c-kit antibody, optionally wherein the anti-c-kit antibody is JSP191.

[0291] In a related aspect, the disclosure provides pharmaceutical compositions, unit dosage forms, and kits comprising one or more doses of an antigen-binding fragment of an anti-c-kit antibody, wherein the antigen-binding fragment is a $F(ab')_2$ (e.g., a JSP191 $(Fab')_2$). In certain embodiments, each of the one or more doses comprises about 14.5 mg to about 200 mg or about

20 mg to about 500 mg of the antigen-binding fragment, optionally about 14.5 mg to about 175 mg, about 20 mg to about 150 mg, about 25 mg to about 250 mg, about 35 mg to about 240 mg, about 35 mg to about 180 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, or about 240 mg of the antigen-binding fragment. In certain embodiments, the kit comprises one or more doses comprising of about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 150 mg, about 180 mg, about 200 mg, about 250 mg, about 300 mg, or about 350 mg of the antigen-binding fragment. In certain embodiments, the kit comprises one or more doses comprising about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 200 mg, about 220 mg, about 240 mg, about 260 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, about 360 mg, about 380 mg, about 400 mg, about 450 mg, or about 500 mg of the antigen-binding fragment. (e.g., a JSP191 (Fab')₂). In particular embodiments, kit comprises a single, high dose in an amount sufficient to administer to the subject about 0.3 mg/kg to about 3.0 mg/kg, about 0.4 mg/kg to about 4.0 mg/kg, about 0.5 mg/kg to about 4 mg/kg, about 0.5 mg/kg to about 3 mg/kg, about 0.67 mg/kg to about 3 mg/kg, about 1 mg/kg to about 4 mg/kg, or about 2 mg/kg to about 4 mg/kg, e.g., about 0.5 mg/kg, mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 2.5 mg/kg, about 3 mg/kg, about 3.5 mg/kg, about 4 mg/kg, about 4.5 mg/kg, or about 5 mg/kg of the antibody or fragment thereof (e.g., a JSP191 (Fab')₂).

[0292] In certain embodiments, the anti-c-kit antibody comprises five or more complementarity-determining regions (CDRs) present in a monoclonal antibody selected from the group consisting of: SR-1, JSP191, MGTA-117, FSI-174, CDX-0159, 8D7, K45, 104D2, CK6, AB249, YB5.B8, AF-2-1, AF11, AF12, AF112, AF-3, AF-1-1, NF, NF-2-1, NF11, NF12, NF112, NF-3, HF11, HF12, and HF112, optionally wherein the antibody is an IgG antibody. In particular embodiments, the anti-c-kit antibody comprises five or more complementarity-determining regions (CDRs) present in a humanized version of a monoclonal antibody selected from the group consisting of: ACK2, ACK4, 2B8, 3C11, MR-1, and CD122,

optionally wherein the antibody is an IgG antibody. In particular embodiments, the anti-c-kit antibody comprises the CDRs of an antibody that blocks the binding of stem cell factor (SCF) to stem cell factor receptor (CD117), optionally wherein the antibody is JSP191.

Differentiation Methods

[0293] In certain embodiments, the disclosure provides a method of altering the differentiation pathway of HSCs and/or HSPCs, comprising contacting the cells with a monoclonal anti-c-kit IgG antibody, including but not limited to any of those disclosed herein. In particular embodiments, the monoclonal anti-c-kit IgG antibody comprises five or more of the CDRs present in an antibody that inhibits binding of SCF to c-kit on the cell surface, e.g., five or more of the CDRs present in JSP-191. In particular embodiments, the anti-c-Kit antibody is JSP-191. In particular embodiments, the method results in increased differentiation of the cells along the megakaryocytic lineage. In various embodiments, the cells are contacted with the anti-c-Kit IgG antibody in vitro, ex vivo, or in vivo.

Enumerated Embodiments

[0294] The following are non-limiting enumerated embodiments of certain aspects of the disclosure.

1. A method of treating, inhibiting, or preventing a mast cell-related disease or disorder in a human subject, comprising administering to the human subject an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), wherein the subject is administered:

- a) two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody, and wherein each dose is administered between eight weeks to six months apart; or
- b) one dose of the anti-c-kit IgG antibody, wherein the dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-Kit IgG antibody of the anti-c-Kit IgG antibody.

2. The method of embodiment 1, wherein each dose comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, or about 360 mg of the anti-c-kit IgG antibody.

3. The method of embodiment 2, wherein each dose comprises about 40 mg, about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit IgG antibody.

4. The method of any one of embodiments 1-3, wherein the disease or disorder is selected from the group consisting of: urticaria, chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), chronic idiopathic urticaria (CIU), urticaria pigmentosa, prurigo nodularis, esophagitis (optionally, eosinophilic esophagitis), asthma, anaphylaxis, mastocytosis, mast cell activation syndrome (MCAS), fibrosis, atherosclerosis, allergic diseases and disorders, dermatitis, endometriosis, interstitial cystitis, and inflammatory bowel disease.

5. The method of embodiment 4, wherein the disease or disorder is chronic spontaneous urticaria (CSU), optionally wherein the subject remains symptomatic despite treatment with an antihistamine, and the subject is administered two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody, and wherein each dose is administered between eight weeks to six months apart.

6. The method of embodiment 4, wherein the disease or disorder is chronic inducible urticaria (CIndU), optionally Cold urticaria (ColdU) or Symptomatic Dermographism (SD), and the subject is administered two or more doses of the anti-c-kit IgG antibody, wherein each dose

comprises about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody, and wherein each dose is administered between eight weeks to six months apart.

7. The method of any one of embodiments 1-6, wherein the anti-c-kit antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously.

8. The method of any one of embodiments 1-7, wherein the subject is administered two or more doses of the anti-c-kit IgG antibody, and wherein each of the doses is administered between about eight weeks to about six months apart, between about eight weeks to about four months apart, between about eight weeks to about twelve weeks apart, between about twelve weeks to about six months apart, between about twelve weeks to about four months apart, about 8 weeks apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, or about six months apart, optionally wherein the time interval between each dose varies.

9. The method of any one of embodiments 1-8, wherein the method results in a $UAS7 \leq 6$ or a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90%.

10. The method of any one of embodiments 1-9, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

11. The method of embodiment 10, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

12. A method for selectively depleting mast cells as opposed to hematopoietic stem and progenitor cells (HSPCs) in a subject, the method comprising administering to the subject one or more therapeutically effective doses of an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ

ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNFSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), wherein each dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody.

13. The method of embodiment 12, wherein each dose comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit IgG antibody.

14. The method of embodiment 13, wherein each dose comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit IgG antibody.

15. The method of any one of embodiments 12-14, wherein the anti-c-kit IgG antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously.

16. The method of any one of embodiments 12-15, wherein the subject is administered two or more doses of the anti-c-kit antibody.

17. The method of embodiment 16, wherein each of the doses is administered between eight weeks to one year apart, between eight weeks to six months apart, between eight weeks to four months apart, between twelve weeks to one year apart, between twelve weeks to six months apart, between twelve weeks and four months apart, about 8 weeks apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, about six months apart, eight months apart, about ten months apart, or about one year apart, optionally wherein the time interval between each dose varies.

18. The method of any one of embodiments 12-17, wherein the method results in a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90% and a reduction in HSPCs of less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%.

19. The method of any one of embodiments 12-18, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

20. The method of embodiment 19, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

21. A kit comprising one or more doses of an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), wherein each of the one or more doses comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody.

22. The kit of embodiment 21, wherein each of the one or more doses comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit IgG antibody.

23. The kit of embodiment 22, wherein the kit comprises one or more doses comprising of about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit IgG antibody.

24. The kit of any one of embodiments 21-23, wherein the kit comprises two or more doses of the anti-c-kit IgG antibody.

25. The kit of embodiment 24, wherein each of the two or more doses of the anti-c-kit IgG antibody comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit antibody.

26. The kit of any one of embodiments 21-25, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

27. The kit of embodiment 26, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

28. A method of altering the differentiation pathway of hematopoietic stem cells (HSCs) and/or hematopoietic stem and progenitor cells (HSPCs), comprising contacting the HSCs and/or HSPCs with an anti-c-kit IgG antibody or antigen-binding fragment thereof, wherein the anti-c-kit antibody inhibits binding of stem cell factor (SCF) to c-kit on the cell surface.

29. The method of embodiment 28, wherein the method results in increased differentiation of the cells along the megakaryocytic lineage.

30. The method of embodiment 28 or embodiment 29, wherein the anti-c-kit antibody or antigen-binding fragment thereof comprises at least five CDRs selected from: heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11).

31. The method of any one of embodiments 28-30, wherein the anti-c-kit antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

32. The method of embodiment 31, wherein the anti-c-kit antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

33. Use of an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), for the manufacture of a medicament for treating, inhibiting, or preventing a mast cell-related disease or disorder in a human subject, wherein the subject is administered:

a) two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody, and wherein each dose is administered between eight weeks to six months apart; or

b) one dose of the anti-c-kit IgG antibody, wherein the dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-Kit IgG antibody of the anti-c-Kit IgG antibody.

34. The use of embodiment 33, wherein each dose comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit IgG antibody.

35. The use of embodiment 34, wherein each dose comprises about 40 mg, about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit IgG antibody.

36. The use of any one of embodiments 33-35, wherein the disease or disorder is selected from the group consisting of: urticaria, chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), chronic idiopathic urticaria (CIU), urticaria pigmentosa, prurigo nodularis, esophagitis (optionally, eosinophilic esophagitis), asthma, anaphylaxis, mastocytosis, mast cell

activation syndrome (MCAS), fibrosis, atherosclerosis, allergic diseases and disorders, dermatitis, endometriosis, interstitial cystitis, and inflammatory bowel disease.

37. The use of embodiment 36, wherein the disease or disorder is chronic spontaneous urticaria (CSU), optionally wherein the subject remains symptomatic despite treatment with an antihistamine, and the subject is administered two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody, and wherein each dose is administered between eight weeks to six months apart.

38. The use of embodiment 36, wherein the disease or disorder is chronic inducible urticaria (CIndU), optionally Cold urticaria (ColdU) or Symptomatic Dermographism (SD), and the subject is administered two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody, and wherein each dose is administered between eight weeks to six months apart.

39. The use of any one of embodiments 33-38, wherein the anti-c-kit antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously.

40. The use of any one of embodiments 33-39, wherein the subject is administered two or more doses of the anti-c-kit IgG antibody, and wherein each of the doses is administered between about eight weeks to about six months apart, between about eight weeks to about four months apart, between about eight weeks to about twelve weeks apart, between about twelve weeks to about six months apart, between about twelve weeks to about four months apart, about 8 weeks

apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, or about six months apart, optionally wherein the time interval between each dose varies.

41. The use of any one of embodiments 33-40, wherein the method results in a $UAS7 \leq 6$ or a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90%.

42. The method of any one of embodiments 33-41, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

43. The use of claim 42, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

44. The use of an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), for the manufacture of a medicament for selectively depleting mast cells as opposed to hematopoietic stem and progenitor cells (HSPCs) in a subject, the method comprising administering to the subject one or more therapeutically effective doses of an wherein each dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody.

45. The use of embodiment 44, wherein each dose comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit IgG antibody.

46. The use of embodiment 45, wherein each dose comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, about 280 mg, or about 360 mg of the anti-c-kit IgG antibody.

47. The use of any one of embodiments 44-46, wherein the anti-c-kit IgG antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously.

48. The use of any one of embodiments 44-47, wherein the subject is administered two or more doses of the anti-c-kit antibody.

49. The use of embodiment 48, wherein each of the doses is administered between eight weeks to one year apart, between eight weeks to six months apart, between eight weeks to four months apart, between twelve weeks to one year apart, between twelve weeks to six months apart, between twelve weeks and four months apart, about 8 weeks apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, about six months apart, eight months apart, about ten months apart, or about one year apart, optionally wherein the time interval between each dose varies.

50. The use of any one of embodiments 44-49, wherein the method results in a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90% and a reduction in HSPCs of less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%.

51. The use of any one of embodiments 44-50, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

52. The use of embodiment 51, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

EXAMPLES

Example 1

BRIQUILIMAB PREVENTS PASSIVE SYSTEMIC ANAPHYLAXIS IN MICE EXPRESSING CHIMERIC HUMAN/MOUSE CD117

[0295] Stem Cell Factor (SCF) signaling through c-Kit (CD117) plays a key role in mast cell differentiation and survival. Briquilimab, a humanized aglycosylated monoclonal antibody targeting CD117, blocks SCF binding to CD117 and SCF/CD117 signaling, leading to apoptosis of mast cells. As diagrammed in FIG. 5, the SCF/CD117 pathway is essential for mast cell function and survival.

[0296] Briquilimab was evaluated in a mouse model of IgE-induced passive systemic anaphylaxis (PSA). C-Kit antibodies designed against human receptor do not bind to wild type mouse c-Kit, so a transgenic mouse model with a chimeric CD117 containing the human c-Kit ectodoman and the mouse c-Kit intracellular domain was developed to allow for direct in vivo testing of c-Kit antibodies, including JSP191. The human extracellular domain binds to both JSP191 and mouse stem cell factor (SCF), and the mouse intracellular domain retains normal signaling. Transgenic mice expressing only chimeric CD117 (h/mCD117), consisting of human extracellular and mouse intracellular regions of CD117 in lieu of wild-type mouse CD117, were generated. The pharmacokinetics, pharmacodynamics, and effect of briquilimab on PSA response were evaluated in the h/mCD117 mice.

[0297] Chimeric h/mCD117 was responsive to mouse SCF and was recognized by briquilimab. Treatment with briquilimab (5, 10, and 25 mg/kg, I.V.) in h/mCD117 mice caused transient modest decreases in peripheral blood counts and transient depletion of CD117 expressing hematopoietic stem cells. The pharmacokinetic clearance of briquilimab in the serum was dose dependent in a nonlinear manner.

[0298] Briquilimab prevented IgE-dependent anaphylaxis reactions in a h/mCD117 mouse model. The experimental schema for evaluation of PSA in h/mCD117 mice administered with one-time briquilimab (25 mg/kg IV) compared to briquilimab untreated controls is shown in FIG. 6A. PSA challenge at the specified timepoints post-briquilimab comprised of administration of α -dinitrophenol (DNP)-IgE IP followed by administration of DNP-HAS (human serum albumin) IV, which can crosslink DNP-IgE. The core body temperature and clinical signs (Clinical Anaphylaxis Score) were monitored over time after PSA challenge at the specified timepoints post-briquilimab. As shown in FIG. 6B, while briquilimab untreated mice (line with squares) showed significant drops of core body temperature (hypothermia) in

response to PSA challenge, briquilimab treated mice (line with triangles) were partially to completely protected from severe hypothermia at 1-4 weeks after briquilimab treatment. The line with squares represents animals that received neither briquilimab nor PSA challenge, and only received isofluorane. FIG. 6C shows that clinical anaphylaxis scores correlated with severity of hypothermia.

[0299] Briquilimab treatment with 5 mg/kg, 3 times per week for three weeks, followed by IgE-induced PSA challenge, led to reduced anaphylactic response.

[0300] Notably, briquilimab treatment with a single 25 mg/kg dose two weeks before PSA challenge completely prevented anaphylactic response, suggesting a single high dose of briquilimab effectively blocks PSA response in h/mCD117 mice (FIG. 4).

[0301] MC depletion in various tissues was assessed after one-time administration of briquilimab intravenously (IV) in h/mCD117 mice. Mast cells were detected by toluidine blue staining of tissue sections. As shown in FIG. 7, differential mast cell depletion and recovery kinetics after briquilimab were observed in various tissues of h/mCD117 mice. FIG. 7A shows mast cell numbers from ear skin, stomach, and tongue in h/mCD117 mice at 1-4 weeks after one-time briquilimab 25 mg/kg IV compared to untreated controls (left bar). FIG. 7B shows representative images of mast cells (stained dark purple indicated by red arrows) from stomach.

[0302] This study demonstrates that briquilimab is a promising treatment option for mast cell-mediated disorders, including but not limited to anaphylaxis.

Example 2

BRIQUILIMAB PREVENTS IgE-INDEPENDENT ANAPHYLAXIS IN MICE EXPRESSING CHIMERIC HUMAN/MOUSE CD117

[0303] Stem Cell Factor (SCF) signaling through c-Kit (CD117) plays a key role in mast cell survival, and inhibition of this pathway has the potential to treat mast cell-related disorders. Briquilimab, a humanized aglycosylated monoclonal antibody targeting CD117, blocks SCF binding to CD117 and SCF/CD117 signaling, leading to apoptosis of mast cells. As diagrammed in FIG. 8, the SCF/CD117 pathway is essential for mast cell function and survival. Drugs or ligands binding to MRGPRX2 on mast cells can induce MC degranulation and pseudoallergic reactions. Blocking SCF/CD117 signaling with briquilimab induces MC apoptosis and may provide protection from severe anaphylactic reactions.

[0304] Briquilimab was evaluated in a mouse model of IgE-independent Mrgprb2-mediated anaphylactoid reactions. Transgenic mice expressing only chimeric CD117 (h/mCD117),

consisting of human extracellular and mouse intracellular regions of CD117 in lieu of wild-type mouse CD117, were generated.

[0305] Briquilimab ameliorated C48/80 mediated anaphylactoid reactions in a h/mCD117 mouse model. The experimental schema for evaluation of C48/80 mediated anaphylactoid reactions in h/mCD117 mice administered with one-time briquilimab (25 mg/kg IV) compared to briquilimab untreated controls is shown in FIG. 9A. One-time briquilimab (25 mg/kg IV) was administered to h/mCD117 mice compared to briquilimab untreated controls. The core body temperature and clinical signs (Clinical Anaphylaxis Score) were monitored over time after 5 mg/kg C48/80 IV administered at the specified timepoints post-briquilimab. As shown in FIG. 9B, while briquilimab untreated mice (line with squares) showed significant drops in core body temperature (hypothermia) in response to C48/80, briquilimab treated mice (line with triangles) were partially to completely protected from severe hypothermia at 2 and 3 weeks after briquilimab treatment. Protection from anaphylactoid reactions was not observed at 4 weeks post-briquilimab. Line with circles represents animals that received neither briquilimab nor C48/80, and only received isofluorane. As shown in FIG. 9C, clinical anaphylaxis scores correlated with severity of hypothermia.

[0306] Mast cell (MC) depletion in various tissues was assessed after one-time administration of briquilimab intravenously (IV) in h/mCD117 mice. Mast cells were detected by toluidine blue staining of tissue sections. As shown in FIG. 10, differential mast cell depletion and recovery kinetics after briquilimab were observed in various tissues of h/mCD117 mice. FIG. 10A shows mast cell numbers from ear skin, stomach, and tongue in h/mCD117 mice at 1-4 weeks after one-time briquilimab 25 mg/kg IV compared to untreated controls (left bar). FIG. 10B shows representative images of mast cells (stained dark purple indicated by red arrows) in ear skin.

[0307] This study demonstrates that briquilimab is a promising treatment option for non-IgE-mediated mast cell-mediated disorders, including but not limited to anaphylaxis.

Example 3

BRIQUILIMAB EFFECTIVELY TREATS EPICUTANEOUS ALLERGEN-INDUCED ATOPIC DERMATITIS IN MICE EXPRESSING CHIMERIC HUMAN/MOUSE CD117

[0308] Stem cell factor (SCF) signaling through c-Kit (CD117) is crucial in mast cell (MC) growth, differentiation, migration, survival, and activation. Inhibition of this pathway with briquilimab, a humanized aglycosylated monoclonal antibody against CD117 that potently

inhibits SCF signaling, has the potential to treat MC-mediated diseases, including atopic dermatitis (AD).

[0309] In transgenic C57BL/6 mice expressing chimeric CD117 (h/mCD117), consisting of human extracellular and mouse intracellular domains of CD117 in lieu of wild-type mouse CD117, AD was induced on back skin by epicutaneous (e.c.) sensitization (days 1-4) and challenge (days 15-18) using house dust mite antigen and Staphylococcal enterotoxin B (HDM/SEB). 50 mg/kg briquilimab was administered intraperitoneally either on day 6 to evaluate AD prophylaxis or on day 21 to evaluate AD therapeutic treatment. Control mice were administered PBS on day 6 or 21. The skin eruption score (ES), scaling score (SS), post-inflammatory hyperpigmentation score (HS), and skin histology were assessed on day 20 (prophylaxis model) or day 37 (therapeutic model).

[0310] In control hmCD117 mice, briquilimab depleted skin MCs by 82% by day 2 ($P < 0.05$). HDM/SEB hmCD117 mice exhibited significant skin eruption, scaling, and hyperpigmentation on day 20, as well as increased dermal MCs (258 ± 30 vs. control $180 \pm 4/\text{mm}^2$, $P < 0.05$) and inflammatory leukocytes (1645 ± 168 vs. control $56 \pm 4/\text{mm}^2$, $P < 0.05$). Prophylactic treatment with briquilimab of HDM/SEB h/mCD117 mice on day 6 led to decreased dermal MCs (103 ± 56 vs. untreated $258 \pm 30/\text{mm}^2$, $P < 0.05$), and decreased inflammatory leukocytes (519 ± 122 vs. untreated $1645 \pm 168/\text{mm}^2$, $P < 0.05$), as well as marked improvements in skin ES (1 ± 0.5 vs. untreated 2.8 ± 0.3 , $P < 0.05$), SS (0.3 ± 0.3 vs. untreated 2.7 ± 0.3 , $P < 0.05$), and HS (0 ± 0 vs. untreated 3.7 ± 0.6 , $P < 0.05$), suggesting that briquilimab can prevent development of AD. Importantly, therapeutic treatment with briquilimab on day 21 in HDM/SEB hmCD117 mice, after AD was established, also led to improved skin ES by 85%, SS by 80%, and HS by 95% on day 37, accompanied by a 70% decrease in dermal mast cells and a 90% reduction in dermal inflammatory leukocytes ($P < 0.05$ for all measures), indicating that briquilimab can reverse AD pathology.

[0311] This study demonstrates that briquilimab is a promising treatment option for treatment of allergic reactions, including but not limited to atopic dermatitis.

Example 4

BRIQUILIMAB PREVENTS ALLERGEN-INDUCED ALLERGIC ASTHMA IN MICE EXPRESSING CHIMERIC HUMAN/MOUSE CD117

[0312] Stem cell factor (SCF) signaling through c-Kit (CD117) is crucial in mast cell (MC) growth, differentiation, migration, survival, and activation. Inhibition of this pathway with briquilimab, a humanized aglycosylated monoclonal antibody against CD117 that potently

inhibits SCF signaling, has the potential to treat MC-mediated diseases, including allergic asthma.

[0313] Pharmacokinetic clearance of briquilimab was determined in transgenic C57BL/6 mice expressing chimeric CD117 (h/mCD117), consisting of human extracellular and mouse intracellular domains of CD117 in lieu of wild-type mouse CD117. h/mCD117 mice received a single dose of intravenous briquilimab (5 mg/kg, 10 mg/kg, or 25 mg/kg), and briquilimab serum concentration was determined at days 3, 4, 6, and 10 following administration of briquilimab. As shown in FIG. 11, pharmacokinetic clearance of briquilimab, at all evaluated dose levels, was faster in h/mCD117 mice compared to non-human primates (Kwon et al, Blood. 2019;133:2014). The 25 mg/kg briquilimab dose in h/mCD117 mice corresponds to about 2 mg/kg in human, as determined by allometric scaling.

[0314] The ability of briquilimab to prevent and treat asthma was examined in h/mCD117 mice according to the prophylactic and therapeutic models shown in FIG. 12. In the prophylactic model, mice were sensitized i.n. with cockroach allergen (CRA) (10 mcg/0.03 mL) at Day 1 and Day 2. The mice were then treated with briquilimab (60 mg/kg, i.p.) on Day 3, and subjected to CRA i.n. challenge on Days 15, 18, and 21, followed by necropsy on Day 22. In the therapeutic model, mice were sensitized i.n. with cockroach allergen (CRA) (10 mcg/0.03 mL) at Day 1 and Day 2, and then subjected to CRA i.n. challenge on Days 15, 18, and 21, followed by treatment with briquilimab (25 mg/kg, i.p.) on Day 22, CRA i.n. challenge (10 mcg/0.03 mL) on Day 24, and necropsy on Day 25. The cockroach antigen-induced model is a prevalent preclinical tool for asthma, as it exhibits several major features of the disease, including airway hyperresponsiveness to methacholine, airway inflammation, and remodeling.

[0315] Prophylactic briquilimab (Briq) treatment inhibited the development of airway inflammation in h/mCD117 mice following CRA sensitization and challenge (FIG. 13). In addition, 19 days after one-time briquilimab preventive treatment, CRA-sensitized and challenged h/mCD117 mice exhibited significantly decreased numbers of mast cells in the lung and back skin (FIG. 14).

[0316] One-time therapeutic briquilimab treatment prevented recurrence of asthma exacerbation following allergen exposure in h/mCD117 mice. Three days post-briquilimab, mice exhibited significantly decreased airway inflammation (including neutrophilic infiltration) and pulmonary resistance following exposure to allergen (FIG. 15). In addition, three days after one-time therapeutic briquilimab treatment, h/mCD117 mice exhibited significant decreases in the numbers of mast cells in the lung and back skin following allergen exposure (FIG. 16).

[0317] This study demonstrates that briquilimab can deplete mast cells in both inflamed (lung) and non-inflamed tissue (back skin) in an allergen-induced asthma model elicited in h/mCD117 mice. The study demonstrates that briquilimab exhibits both prophylactic and therapeutic benefits in the treatment of allergic reactions.

Example 5

JSP191 DEPLETES LUNG MAST CELLS IN PRIMATES

[0318] This example tested the efficacy of JSP191 in reducing tryptase-positive and c-KIT-positive skin mast cells.

Methods

Pharmacokinetics and Pharmacodynamics Study of Briquilimab in African Green Monkeys

[0319] Seventeen naive sexually mature male African green monkeys were divided into 4 dosing groups (4 or 5 animals/group) by body weight randomization. On day 0, each animal received 8 skin punctures on the back. Within two hours after the wounding, the 4 dosing groups received a single SC administration of briquilimab at 0 (placebo control), 0.1, 1, and 10 mg/kg, respectively. Serial PK samples were collected up to 35 days for all animal groups. Skin biopsy samples around the incisional wounds were collected up to day 49 using a composite approach for all animal groups. Testes and colon samples were collected from each animal on day 49 for spermatogenesis toxicity and colon MC assessment. Predose and day 49 serum samples were collected for clinical immunology analysis. Briquilimab concentrations were measured using an enzyme linked-immunosorbent assay (ELISA) with a lower limit of quantification (LLOQ) of 10 ng/mL. Individual pharmacokinetic parameters were estimated using noncompartmental methods. Pharmacokinetics-pharmacodynamics modeling was conducted. The skin MC density was determined by an automatic laser scanning cytometry method. Additional quantification by anti-Tryptase immunohistochemistry (IHC) assay confirmed that data were comparable between two methods. Testes and colon samples were formalin fixed, embedded in paraffin, sectioned and stained with Hematoxylin and Eosin and by IHC for c-Kit and Tryptase.

MC Analysis in a Repeat-Dose Pharmacology Study of Briquilimab in African Green Monkeys

[0320] For evaluation of skin MCs in wounded skin, adult male African green monkeys were anesthetized, each wound was created using a sterile disposable 3-mm skin punch biopsy tool and then closed with a single suture on day 0. Briquilimab was administered SC to animals at dosages of 0 (vehicle/placebo), 0.3, 1, or 3 mg/kg once a week for 4 weeks. Skin biopsies encompassing the entire wounded skin area from 2 of the 3-mm skin wound sites for each

monkey were collected using a 6-mm skin punch biopsy tool on days 0, 4, 7, 14, and 21. Additional tissue samples including unperturbed skin, lung, and colon were collected from most animals at the study termination on day 28. Additionally, lung and colon were collected from 1 low-dose, 1 mid-dose, and 1 control animal at necropsy after a 3-month treatment-free period. The tissue samples were fixed in 10% neutral buffered formalin for 24 hours and then transferred to 70% ethanol. Fixed tissue samples were trimmed, dehydrated through graded ethyl alcohol solutions, embedded in paraffin, cut into 4-mm sections. MCs were visualized by Astra blue histochemical staining or by immunohistochemistry using anti-CD117, anti-tryptase, or anti-chymase antibodies.

Toxicity and Toxicokinetics

[0321] To evaluate the toxicity and determine the toxicokinetics of briquilimab, male and female cynomolgus monkeys (*Macaca fascicularis*) 5 to 7 years old at start of dosing, were assigned to four groups (six animals/sex/group). Animals were given the placebo control (vehicle only) or Briquilimab at dose levels of 1, 10, and 300 mg/kg of body weight/dose (mg/kg/dose) at a dose volume of 4.03 ml/kg once weekly via SC injection for 1 month (total of four doses). To assess the reversibility, persistence, or delayed occurrence of any effects, animals were examined after a 4-month treatment-free phase. Assessment of toxicity included clinical signs, body weights, qualitative food consumption, physical and ophthalmic examinations, electrocardiology evaluations, and clinical and anatomic pathology. Blood samples were also collected for toxicokinetics and antibody analysis from all animals on Days 1 and 22 of the dosing phase, during predose and approximately 2, 8, 24, 48, 96, and 168 hours post-dose period. Blood samples were also collected predose on Day 15 of the dosing phase. In addition, one blood sample from each animal was collected during the treatment-free phase on Treatment-Free Days 14, 28, 42, 56, 70, 84, 98 and 113 (Study Days 43, 57, 71, 85, 99, 113, 127, and 142, respectively). Histology and MC evaluation was performed as described earlier.

Briquilimab depletes MCs in NHPs

[0322] After a single SC administration (0.1 to 10 mg/kg) of briquilimab to adult African green monkeys, dose-dependent log-linear clearance with the median t_{max} ranging from 1 to 3 days occurred. (Fig. 17A). C_{max} increased more than dose proportionally from 0.1 to 1 mg/kg and nearly dose proportionally from 1 to 10 mg/kg, respectively. AUC_{last} increased more than dose proportionally in the dose range studied, suggesting non-linear saturable disposition of briquilimab in African green monkeys (Fig. 17B). PK studies of single IV and SC doses (0.1 to 10 mg/kg) of briquilimab were also evaluated in cynomolgus monkeys (data not shown).

After briquilimab SC administration, the bioavailability was approximately 72% and 56% at 1 and 10 mg/kg, respectively.

[0323] After 49 days, colon submucosa MCs were significantly decreased, compared to placebo control (Figs. 17C and 17D). MCs adjacent to wounded skin initially declined after injury regardless of briquilimab treatment. Subsequently, the MC number rebounded in the control group, whereas animals treated with 10 mg/kg dose maintained suppressed numbers of MCs at the wound site until necropsy on Day 49. At lower doses (0.1 and 1 mg/kg) of briquilimab, skin MC suppression was more modest and MC number increased with tissue healing to a lesser degree than control group (Fig. 17E).

[0324] Similar dose-dependent decreases in colon submucosa, interstitial and peribronchial lung MCs were observed after repeat dosing of briquilimab (0.3 to 3 mg/kg/dose once weekly for 4 weeks) in African Green monkeys on Day 28 (Figs. 17F, 17I-17L). Decreases were also observed in dermal MCs stimulated to migrate into adjacent wounded skin area by all three doses of briquilimab at 21 days after wounding, compared to placebo control (Figs. 17G, 17H). Following a 3-month treatment-free period in a subset of animals, peribronchial MCs returned to normal for both 0.3 and 1 mg/kg doses while interstitial MCs were still mostly decreased (data not shown). A similar trend toward recovery of MC numbers was observed in the colon (data not shown). In conclusion, treatment of African green monkeys with briquilimab resulted in decreased numbers of resident tissue MC populations in colon, wounded skin and lung.

Briquilimab is generally well-tolerated in NHPs

[0325] GLP-compliant toxicology studies in cynomolgus monkeys were completed to evaluate 1-month weekly SC injection of briquilimab (1, 10, or 300 mg/kg/dose) with a 4-month treatment-free phase and 6-month weekly SC injection of briquilimab (1, 30, or 300 mg/kg/dose) with a 32-week treatment-free phase. Briquilimab was well-tolerated with no significant changes in body weight, clinical chemistry, ophthalmology, electrocardiography, respiratory or neurological function during the treatment and recovery period in both studies. Observations attributed to briquilimab included a transient dose-dependent reduction in absolute reticulocyte count present at Day 15 of the dosing phase at all dose levels and a moderate reduction in red blood cell mass at the end of the dosing phase in animals that received 10 or 300 mg/kg/dose (Figs. 18A-18C), but no correlative bone marrow cytologic findings were observed. On Day 107 of the 4-month treatment-free recovery phase in the 1-month toxicology study, gray and coarse haircoat was observed only at the briquilimab injection site in 2 animals from the highest dose group (300 mg/kg/dose) who were subsequently monitored for clinical signs. In the 6-month toxicology study, pale skin was noted

in all animals given 30 or 300 mg/kg/dose on the appendages starting on Day 141 during the 6-month dosing phase and persisted until scheduled necropsy (treatment-free day 225, Study Day 407). The fur was also lighter in some animals given 30 or 300 mg/kg/dose. The most common sites for the pale fur were the trunk and appendages in males. The pale fur was less common in females but when observed, was mostly on the appendages. Lighter colored fur correlated microscopically with decreased pigment in hair follicles and/or epidermis.

[0326] At the end of the dosing phase, testis and epididymis weights were lower in all male animals given briquilimab in both studies. In the 1-month toxicology study, testis effects in the 1 and 10 mg/kg/dose groups had completely reversed at the end of the 4-month treatment-free phase, and at the 300 mg/kg/dose, the testis had not yet returned to normal but appeared to be recovering. In the 6-month toxicology study, testis and epididymis weights returned to normal at the end of the 32-week treatment-free phase. Additionally, after a single dose of 1 or 10 mg/kg briquilimab SC in African Green monkeys, spermatogenesis was noted to be transiently inhibited, with evidence of recovery before day of necropsy, at 49 days after briquilimab. Characterization of the relationship between PK exposure and the transient inhibition of spermatogenesis suggest that spermatogenesis recovers after serum concentration briquilimab falls below an inhibitory threshold approximately between 0.1 and 1 mg/ml.

[0327] It is noteworthy, that the dose and schedule used in the chronic toxicology studies are significantly higher, leading to sustained chronic drug exposure, constantly saturating c-Kit on all tissues leading to adverse finding described in the study. Subsequent administration of briquilimab in the healthy volunteer and clinical trials examined lower drug exposures and intermittent dosing (Q8 and Q12 weekly) which may mitigate potential unwanted effects from c-Kit blockade on tissues other than MCs.

Example 6

BRIQUILIMAB DEPLETES SKIN MAST CELLS IN HUMANS

[0328] This example tested the efficacy of briquilimab in reducing mast cells in a single ascending dose study in healthy volunteers.

[0329] The study was designed to enroll 12 dose cohorts, including 11 sequential SC cohorts and 1 intravenous (IV) cohort. The dosages of briquilimab administered in the study were 0.2, 0.7, 2, 5, 10, 20, 42, 84, 158 and 280 mg SC. The first SC cohort (cohort 1) and the IV cohort (cohort 7) consisted of 6 participants randomized to receive a single dose of briquilimab or placebo in a 2:1 ratio. Participants in the remaining cohorts consisted of eight participants randomized to receive a single dose of briquilimab or placebo in a 3:1 ratio. A sentinel dosing

paradigm was used for cohorts 1 to 3 and 5 to 12; 1 participant was administered briquilimab and the other was administered a matched dose of placebo. Sentinel participants were observed for safety signals for 48 hours (cohorts 1 to 3 and 5 to 10) or 43 days (cohorts 11 to 12) postdose before the remaining participants in each cohort were dosed.

[0330] Starting with cohort 5 (10 mg SC), a pharmacodynamic (PD) assay was incorporated to assess the magnitude and variability of MC infiltration via punch biopsy. In cohorts 5 to 11, all participants received one 3 mm punch biopsy each on the upper left and right buttocks (study day -1), a 6 mm punch biopsy on day 7 encompassing the 3-mm biopsy on the left, and a 6-mm biopsy on day 29 encompassing the 3-mm biopsy on the right (total of 4 punch biopsies). In the biopsied tissue samples, MCs were enumerated using 2 confirmatory techniques. An automated laser scanning cytometry assay was used to measure tryptase-positive cells per unit area of tissue sections, and a pathologist counted cluster of differentiation (CD117)-positive MCs using manual morphometric analysis.

[0331] Serial blood samples were collected and serum concentrations of briquilimab were determined using a validated assay. Briquilimab pharmacokinetic parameters were estimated by noncompartmental analysis using WinNonlin. Serum samples for anti-briquilimab antibodies were collected predose and at the end of study and analyzed for binding and neutralizing antibodies.

Briquilimab administered to healthy human volunteers (HVs) was generally well-tolerated and depleted skin MCs

[0332] The population enrolled across all treatment groups (67 receiving briquilimab SC and 25 receiving placebo) was generally well balanced with no baseline factor(s) creating notable differences in the analyses. In the SC dosing cohorts, 14 placebo- and 41 briquilimab-treated participants were evaluable for PD analysis.

[0333] Briquilimab serum concentrations were below the lower limit of quantitation after SC administration of 0.2 mg. Mean serum briquilimab concentration-time profiles at other dose levels are shown in Fig. 19A and pharmacokinetic parameters are presented in Figs. 19B (briquilimab C_{max}) and FIG. 19C (briquilimab AUC_{last}). A total of 14% (10/71) of participants had anti-briquilimab antibodies, all occurring at doses ≥ 20 mg; however, there was no clear association between dose and the presence of anti-briquilimab antibodies. Six of these participants had neutralizing anti-briquilimab antibodies at Day 57. Overall, binding, non-neutralizing antibodies had no apparent impact on the punch biopsy wound model in any participant.

[0334] Participants who received placebo, had c-Kit-positive MCs present at the skin wound periphery on Day 7 only, with movement into the wound bed by Day 29. In briquilimab-treated participants, MC numbers were decreased at Day 7 compared to baseline at all dose levels, however, MC numbers increased from Day 7 to Day 29 at low doses (0.5 to 42 mg) consistent with tissue healing (Fig. 19E). At the 84 mg dose, a consistent decrease in the number of MCs at the wound site was maintained up to Day 29 in 5 of 6 participants, while MC counts at the highest doses (158 and 280 mg) continued to decrease at Day 29 below the Day 7 levels (Figs. 19D and 19E) indicating a dose-dependent effect and impaired MC recovery. These data are consistent with those observed in NHPs (Fig. 17). Briquilimab treatment resulted in significant and lasting effects in reducing both tryptase-positive and c-KIT-positive skin mast cells at all SC doses of 84 mg (about 1 mg/kg) or higher (Fig. 19E). Interestingly, so long as the dose was higher than 0.8 mg/kg, the mast cell-depleting activity of the antibody was substantial (about 60% reduction or more). A single subcutaneous dose at or about 80 mg potentially depleted mast cells in the skin of the healthy volunteers. C_{max} was reached at about day 5. Depletion began occurring as early as seven days following dosing, with robust depletion observed at day 29.

[0335] Overall, a single dose of briquilimab administered SC was generally well tolerated in healthy volunteers. AEs were reported for 94 of 96 participants (98%). There were no deaths, serious adverse events (SAEs), or AEs leading to withdrawal. During the study, dysgeusia was identified as a clinically significant AE, occurring in 5 of 6 participants given briquilimab at 280 mg. All events of dysgeusia occurred between 8 and 23 days after dosing, were mild to moderate in severity, and were considered treatment-related by the investigator. All 5 events of dysgeusia resolved between 5 and 58 days after symptom onset.

[0336] The most common ($\geq 10\%$) treatment-emergent AEs (TEAEs) across briquilimab (SC) dose groups were headache, nausea, URI, dizziness, and lethargy. All TEAEs were $\leq$ Grade 2. Of note, 5 adverse events (nausea, upper respiratory tract infection [URI], dizziness, back pain, and lethargy) reported in $\geq 10\%$ of participants receiving briquilimab occurred more than twice as frequently compared to placebo, however there was no clear association with briquilimab dose. The occurrence of treatment-related AEs (TRAEs) was similar between briquilimab (85%) and placebo (72%). Other than dysgeusia, there was no obvious increase in TRAE frequency between briquilimab and placebo.

[0337] Dose-dependent changes in laboratory parameters were observed, mostly occurring at 42 mg of briquilimab and above. These changes were decreases in red cell indicators (reticulocyte counts, hemoglobin, hematocrit, and RBC counts), decrease in platelet counts, low neutrophil count compared to placebo, and a higher incidence of WBCs below the limit of

normal compared to placebo (Fig. 20). Overall, the observed changes in laboratory parameters were more evident at higher doses (i.e., were largely dose dependent), were asymptomatic and transient in nature, were non-severe and were consistent with nonclinical findings and the expected mechanism of action, as c-Kit is expressed early in hematopoiesis.

Example 7

BRIQUILIMAB INHIBITS MAST CELL DEGRANULATION AND SURVIVAL

[0338] Briquilimab is a humanized IgG1 monoclonal antibody with an N297Q modification leading to an aglycosylated Fc domain. Briquilimab binds to human and monkey c-Kit with a KD of < 5 pM, but exhibits essentially no binding to mouse or dog c-Kit. Briquilimab binds to human c-Kit in the SCF ligand binding domain and inhibits SCF binding to c-Kit. In contrast, JSP084 is a humanized IgG1 monoclonal antibody that binds to c-Kit at its dimerization domain and inhibits dimerization of c-Kit monomers. While both briquilimab and JSP084 bind to c-Kit expressed on SCF-dependent M-07e cells (Fig. 21A), briquilimab binds with slightly higher affinity than JSP084 (EC90 = 9.4 nM and 11.1 nM, respectively).

[0339] The effects of briquilimab, JSP084, and imatinib on SCF/c-Kit signaling and MC degranulation and survival, ADCC/CDC was evaluated using M-07e, Ba/F3, primary human mast cells and modified Jurkat effector cells.

Methods

c-Kit antibodies

[0340] Briquilimab is an aglycosylated and humanized IgG1 monoclonal antibody against human c-Kit. JSP084 is a comparative reagent generated from sequences in publicly available patent publications, in in-house experimental comparison. The former binds to the ligand binding domain of c-Kit while the latter binds to its dimerization domain.

Antibody Binding Assay

[0341] The M-07e cells expressing the native human c-Kit were obtained from the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures and grown according to distributor's recommendation. 50,000 cells were seeded to each well in a 96-well-plate. Anti-c-Kit antibodies, briquilimab or JSP084 were prepared by 2-fold serial dilutions in serum free RPMI 1640 culture media starting at 100 nM and each diluted antibodies was added to cell-seeded wells and incubated for 30 minutes at 4°C. Following washing, cells were incubated with Alexa Flour 488-labeled anti-human IgG1 secondary antibody (ThermoFisher). Cells were incubated in the dark at 4°C for 30 minutes, washed and resuspended in FACS Buffer (PBS with 5% FBS) containing Sytox Blue or DAPI viability staining solution (ThermoFisher)

for 5 minutes. Cytofluorimetric analysis was conducted using a CytoFLEX flow cytometer (Beckman Coulter). Cells were sorted by scatter properties and separated for single cell analysis using side scatter width vs. side scatter area. Cells were gated on live cells using the Sytox Blue or DAPI viability dye. Antibody binding to cells was quantitated by measuring fluorescent emissions at an excitation wavelength of 488 nm using a 525/40 nm filter. Data analysis was performed using GraphPad Prism. Half maximal effective concentration (EC50) values and EC90 values were calculated with GraphPad Prism using a 4-parameter sigmoidal curve fit (variable slope) using normalized data.

SCF Blocking Assay

[0342] The M-07e cells were plated at 50,000 cells per well in a 96-well-plate and incubated with 2-fold serial dilutions of briquilimab or JSP084 in serum free RPMI medium at 4°C for 1 hour. Then, SCF conjugated with Alexa-647 (ThermoFisher) per manufacturer's instructions were added for 30 minutes at a concentration of 10 ng/mL at 4°C. Flow cytometry data were analyzed as described above, and normalized bound SCF data were fit to a 4-parameter nonlinear regression equation from which IC50 and IC90 values were derived.

c-Kit Receptor Internalization

[0343] The M-07e cells were seeded to wells of tissue culture 96-well plate at 50,000 cells per well in 100 μ L of RPMI 1640, 20% FBS and incubated with 2-fold serial dilutions of briquilimab or JSP084 antibody for 30 minutes at 4°C. Without any washing step, SCF was added to the wells at 10 ng/mL and incubated for 1 h at 37°C. Only media was added to the no SCF control. SCF-induced receptor internalization was measured by applying a non-competing, non-neutralizing antibody to c-Kit (clone 104D2, BioLegend) labeled with phycoerythrin, which was incubated with cells for 30 min at 4°C. After washing with FACS buffer (1X PBS containing 5% FBS), cells were stained with viability dye and flow cytometry data were analyzed as described above. The amount of internalization observed was quantified by comparing the loss in mean fluorescent intensity (MFI) of cells treated with antibodies to MFI of the control (media alone). A second control consisting of SCF and no blocking antibody was used to demonstrate the full extent of endocytosis with ligand alone.

c-Kit and Akt Phosphorylation

[0344] M-07e cells endogenously expressing human c-Kit or Ba/F3 cells transfected with human c-Kit were plated in 96 well plates and serum starved for 30 min or overnight, respectively, and incubated with 2-fold diluted briquilimab, JSP084 or imatinib (Selleck Chemicals) for 30 min at 37°C. Cells were then stimulated with 100 ng/mL of SCF (PeproTech) for 2 or 15 minutes, respectively. Cells were washed, lysed in 1X MSD Tris Lysis Buffer

containing protease and phosphatase inhibitors (Meso Scale Discovery). Lysate concentrations were measured with Pierce 660nm Protein Assay kit (ThermoFisher), normalized and applied to MSD analysis. To measure c-Kit phosphorylation, the well bottom of Multi-array 96-well plates (Meso Scale Discovery) were coated with an anti-c-Kit capture antibody (clone 104D2, Biolegend) and blocked with 5% BSA in Tris wash buffer for 1 hour. Lysates were added and incubated for 1 hour at room temperature, followed by washing and incubation with a SULFO-TAG anti-phosphotyrosine detection antibody (Meso Scale Discovery) for 1 hour. Plates were then washed and incubated with 2x Read Buffer (Meso Scale Discovery) for 5 min and signals were developed following electrochemical stimulation and measured on the MSD QuickPlex SQ120 reader (Meso Scale Discovery). Signals were measured as relative luminescent units (RLUs) and are proportional to the amount of phosphorylated KIT bound in each well. Curves were fitted using a 4-parameter logistic nonlinear regression analysis with weighting using GraphPad Prism. For AKT phosphorylation, Phospho (Ser473)/Total Akt Whole Cell Lysate Kit (Meso Scale Discovery) was used per manufacturer's instructions.

Cell Proliferation

[0345] Cells were plated at a density of 15,000 cells per well in a 96-well cell proliferation assay plate (Corning) in complete media lacking GM-CSF. Briquilimab, JSP084 and imatinib were titrated onto cells, followed by addition of SCF (PeproTech) to a final concentration of 100 ng/mL and incubated for 6 days at 37°C. Cell viability was indirectly measured using Cell Titer Glo 2.0 (Promega). The luminescence of each well was measured immediately by using a microplate reader, SpectroMax. The half maximal concentration (IC50) values and IC90 values were calculated using GraphPad Prism based on normalized data. Log-transformed concentration data were plotted as a function of luminescence. Curve fitting was performed using a four-parameter non-linear regression algorithm, from which IC50 and IC90 values were derived.

Human MC Differentiation

[0346] MC differentiation was performed as described by Radinger et al (1). Briefly, human CD34+ cells were isolated from mobilized peripheral blood with CliniMACS CD34 MicroBeads on the CliniMACS Prodigy (Miltenyi Biotec) and frozen in Cryostor CS10 (Stemcell Technologies, Vancouver, CA). 10×10^6 CD34+ cells were thawed and cultured in MC base media consisting of StemPro-34 SFM plus supplement (Gibco), 2mM L-glutamine, 100U/mL penicillin and 100ug/mL streptomycin. During the first week, 100ng/mL SCF, 100ng/mL IL-6 and 30ng/mL of IL-3 were added to the culture. IL-3 was no longer added after the first week. Cells were expanded for the first two weeks. Starting on week 3, cells

were centrifuged at 450xg for 5 minutes to replace 50% of the spent media with fresh media, then transferred to new flasks. This was repeated weekly. Cultures typically matured into MCs by weeks 7-9 as determined by flow cytometry (>80% CD-117+ FceRI+ out of CD34- cells).

Degranulation and Measurement of β -hexosaminidase Release

[0347] β -hexosaminidase release was measured as described by Radinger et al (2). Briefly, MCs were starved of all cytokines overnight then plated in 96-well plates at 100,000 cells per well. Cells were dosed with antibody as appropriate and incubated in a dry 37°C oven for 90 minutes. As appropriate, cells were incubated with 100ng/mL human IgE for 30 minutes, followed by another 30-minute incubation with 1ug/mL goat anti-human IgE and/or 100ng/mL SCF. To assess released b-hexosaminidase, half of the supernatant was incubated with 0.35% PNAG (p-Nitrophenyl-N-acetyl- β -D-glucosaminide in citrate buffer) for 90 minutes. To determine total b-hexosaminidase, the remaining cells and supernatant were lysed with 0.1% triton then incubated with PNAG for 90 minutes. 400mM glycine buffer was added to all samples and absorbance measured at 405nm with 620nm as reference on the Spectramax plate reader (Molecular Devices, San Jose, CA). Percent b-hexosaminidase release was calculated as a ratio of released vs total absorbance readings. To measure IgE independent degranulation, MCs were treated with IFN γ at a final concentration of 0.15ng/mL, for 40 hours. The degranulation assay was conducted with antibodies as above without the addition of IgE and anti-IgE.

Survival Assay

[0348] 25,000 cells were seeded in 96-well plates with varying doses of antibody in 100uL MC media with SCF and IL-6. Control MCs without antibody were plated in 100uL media with either SCF + IL-6, IL6 only, or no cytokines. All samples were incubated at 37°C for 6 days until assay. Half of each sample was stained with an equal volume of AO/PI (Nexcelom Bioscience, Lawrence, MA) for 5 minutes per manufacturer's protocol. Analysis of the entire well bottom was conducted with an ImageXpress Pico (Molecular Devices, San Jose, CA) at 10x magnification with auto focus. Exposure and intensity were set by testing at least 3 wells. To determine MC purity, the remaining cells were washed with PBS/BSA then stained with 1ug/mL of CD34, CD-117, and 2ug/mL of FceRI antibodies for 20 minutes. Excess antibody was washed off and cells were stained with DAPI before analyzing on the Cytoflex flow cytometer (Beckman Coulter, Brea, CA). Live MC count was calculated by the number of live cells counted by Pico within the mature MC fraction determined by flow cytometry.

ADCC Assay

[0349] ADCC activity was studied in M-07e cells using the Promega ADCC Reporter Bioassay Kit with effector Jurkat cells (Promega, Madison, WI) following manufacturer's instructions. Briefly, 25uL of M-07e cells (75,000 per well) were incubated with 25uL of serially diluted briquilimab or briquilimab Fc-variants and co-cultured with Jurkat cells for 6 hours at 37°C. Plates were removed from the incubator and allowed to equilibrate to room temperature for 15 minutes then incubated in the dark with 75uL of Bio-Glo for 10-30 minutes before measuring luminescence with the Spectramax plate reader (Molecular Devices, San Jose, CA).

CDC

[0350] The M-07e cells with or without 10 mg/mL of protein G were pre-incubated with serially diluted briquilimab at 4°C for 30 minutes, then 10% human complement serum was added to the cells. The heat-inactivated HS was used as negative control. After 24 hours incubation at 37°C, PI was added (2.5 mg/mL). PI positive i.e. non-viable cells were determined by flow cytometry.

Results

Briquilimab inhibits SCF-dependent c-Kit activation

[0351] Briquilimab completely inhibited fluorescently labeled SCF from binding to c-Kit in M-07e cells ($IC_{90} = 11$ nM), whereas JSP084 only partially inhibition of SCF binding, even at the highest concentration evaluated ($IC_{90} = 16921$ nM) (Fig. 21B). Briquilimab also inhibited 87% of SCF-induced c-Kit receptor internalization in M-07e cells ($IC_{90} = 28.1$ nM), whereas JSP084 resulted in 63% inhibition of internalization ($IC_{90} = 51.2$ nM) (Fig. 21C).

[0352] Briquilimab inhibited SCF-dependent c-Kit phosphorylation of M-07e cells more potently relative to JSP084 (86 % and 71%, respectively) at the highest concentrations measured (Fig. 21D). Both briquilimab and JSP084 were significantly more potent ($IC_{50}=7.9$ nM, $IC_{50}=9.6$ nM, respectively) than FDA-approved, small molecule, c-Kit targeting tyrosine kinase inhibitor imatinib ($IC_{50}=364.9$) (Fig. 21D). Relative to briquilimab, JSP084 incompletely blocked SCF binding, SCF-induced c-Kit receptor internalization, and c-Kit phosphorylation, and at low concentrations (1nM), appeared to be agonistic, in M-07e cells (Fig. 21E). Additionally, low concentration of JSP084 led to upregulated phosphorylation of AKT, a downstream kinase of SCF/c-Kit anti-apoptotic signaling, in a Ba/F3 cell line stably transduced to overexpress human c-Kit, whereas briquilimab did not (Fig. 21F).

Briquilimab inhibits MC degranulation and survival

[0353] Briquilimab was more effective than JSP084 at inhibiting SCF-mediated M-07e cell proliferation ($IC_{90} = 35.1$ nM and 97.5 nM, respectively) (Fig. 21G). Briquilimab also completely inhibited SCF-enhanced MC survival in culture (648 pM) to the level of cells cultured without SCF (Fig. 21H). Briquilimab also inhibited 93% of IgE/Fc ϵ R dependent primary MC degranulation ($IC_{50} = 187$ pM), compared to JSP084 which achieved only 79% inhibition ($IC_{50} = 791$ pM) at the highest concentrations of antibody tested (Fig. 21I). These results suggest that briquilimab inhibits primary MC degranulation within hours and MC survival within days more potently than JSP084 in vitro. Direct blocking of SCF binding to c-Kit by briquilimab may be more effective on blocking SCF/c-Kit signaling than inhibiting dimerization of c-Kit.

Aglycosylation abolishes Fc γ R-dependent MC activation

[0354] Theoretically, c-Kit-targeting antibodies could initiate antibody Fc-mediated clustering of Fc γ receptors (Fc γ Rs) on MCs and other Fc-mediated effector functions potentially leading to unwanted MC activation and degranulation and effects on other c-Kit-expressing cells. To eliminate any potential for Fc γ R crosslinking and effector functions, briquilimab was specifically aglycosylated via N297Q modification, which eliminates binding of briquilimab to Fc γ Rs. Compared to Fc-active variants, briquilimab does not bind to any Fc γ Rs and did not lead to any measurable Fc γ R-dependent MC activation and degranulation (Fig. 21J). Briquilimab did not induce Fc γ R-mediated antibody dependent cell mediated cytotoxicity (ADCC) nor complement dependent cytotoxicity (CDC) in both M-07e cells (Fig. 21K) and UT-7 cells (data not shown).

Example 8**Briquilimab Potently Inhibits SCF/c-Kit Signaling, Which Does Not Induce Healthy HSC Apoptosis, But Skews HSC Differentiation Potential**

[0355] Hematopoietic stem cells (HSCs) are responsible for the production of all blood cell lineages). The HSC compartment is tightly regulated by intrinsic and extrinsic signals, including cytokines and growth factors, during both steady state and stress hematopoiesis. The net output of signaling pathways determines the fate of HSC for self-renewal, differentiation, migration, or apoptosis. Stem cell factor (SCF) and its signaling via the c-Kit receptor plays an important role in the regulation of HSC fate. Briquilimab (JSP-191) is a humanized monoclonal antibody that binds to c-Kit and inhibits SCF signaling.

[0356] The molecular basis of briquilimab inhibition of the SCF/c-Kit signaling pathway and its functional impact on healthy human HSC survival, proliferation, and differentiation was examined. Briquilimab binding to c-Kit, phosphorylation and receptor internalization of c-Kit were evaluated using the M-07e cell line, which expresses endogenous SCF-responsive human c-Kit. Healthy long term primary human HSCs (CD34+CD38-CD90+CD45RA-) were sorted from bone marrow mononuclear cells and cultured *ex vivo* in X-vivo media containing Thrombopoietin (TPO), Flt3-ligand (Flt3-L), and SCF, with or without briquilimab. The proliferation, apoptosis, and differentiation of primary human HSCs were monitored by flow cytometry and automated cell imaging.

[0357] As shown in FIGs. 22A-22D, briquilimab blocked SCF binding to c-Kit, SCF mediated c-Kit internalization, and c-Kit phosphorylation in M-07e cells. M-07e cells were incubated with increasing amounts of briquilimab prior to each assay for 30 min to 1 hr. FIG. 22A shows briquilimab binding to c-Kit as detected by Alexa Flour 488 anti-human IgG1 antibody. FIG. 22B shows SCF binding to c-Kit as detected by Alexa-647-conjugated SCF. Cells were further incubated with SCF (10 ng/mL) for 30 min, followed by incubation with briquilimab. Cell surface c-Kit was measured by PE conjugated to a non-competing and non-neutralizing antibody to c-Kit (104D2 clone). Fluorescence was analyzed by flow cytometry (FIG. 22C). Cells were stimulated with SCF (100 ng/mL) for 2 min followed by incubation with briquilimab. After cell lysis, phospho-c-kit levels were detected by the Meso Scale Discovery (MSD) immunoassay platform using an anti-c-Kit capture antibody (clone 104D2) and a SULFO-TAG anti-phosphotyrosine detection antibody (FIG. 22D).

[0358] FIGs. 23A-23B show that briquilimab did not induce apoptosis of healthy HSC. 1000 purified HSC were cultured with TPO (50 ng/mL) and Flt3-L (50 ng/mL) in the presence or absence of SCF (25 ng/mL) and briquilimab (1 mg/mL). Total live cells were counted by PICO automated cell imaging system on the indicated day of *ex vivo* culture (FIG. 23A). Cells were stained with Annexin V and Propidium Iodide (PI) and analyzed by flow cytometry to determine live and Annexin V⁺PI⁺ apoptotic cell numbers (FIG. 23B).

[0359] FIGs. 24A-24D show that briquilimab skews HSC differentiation into an alternative pathway. The cultured HSC were stained with CD34, CD38, CD90, CD45RA, CD123, and c-Kit on the indicated day of *ex vivo* culture, and then analyzed by flow cytometry. FIG. 24A shows the flow cytometry plots of CD34 and CD38 expression and a graph of the fold change of Mean Fluorescence Intensity (MFI) of CD34 and CD38 expression on the cell surface at indicated timepoints are shown. HSC and each progenitor cell number were defined based on cell markers, and the results are shown in FIG. 24B. Multipotent progenitor: MPP

(CD34+CD38-CD90-CD45RA-), Common myeloid progenitor: CMP (CD34+CD38+CD45RA-CD123low), Granulocyte-monocyte progenitor: GMP(CD34+CD38+CD45RA+ CD123low), Megakaryocyte-erythrocyte progenitor: MEP(CD34+CD38+CD45RA-CD123-). FIG. 24C provides a classic scheme of HSC differentiation into the myeloid lineage and expression pattern of CD34 and CD38 on HSC and progenitor cells. FIG. 24D shows the flow cytometry plot of c-Kit expression in each group and a graph of the fold change of c-Kit expression on the cell surface at the indicated timepoints are shown.

[0360] These experiments demonstrate that briquilimab potently blocks SCF/c-Kit signaling by binding to c-Kit, and that the blocking of SCF/c-Kit signaling by briquilimab does not cause HSC apoptosis. In addition, they show that *ex vivo* cultured HSC with SCF, TPO, Flt3-L have the capability to differentiate into different progenitors (CMP, GMP, MEP), as evidenced by increased CD38 expression on differentiated cells by Day 7. Moreover, HSC cultured with SCF, TPO, Flt3-L in the presence of briquilimab differentiated directly into CD34- cells with higher c-Kit expression and without increased CD38 expression by Day 7.

[0361] FIG. 25 provides a hypothetical model of how the blocking of SCF/c-Kit signaling by briquilimab skews HSC towards a distinct alternative HSC differentiation pathway in *ex vivo* culture. Briquilimab binds to c-Kit and blocks SCF/c-Kit signaling that plays an essential role in self-renewal and differential potential. Given previously published findings showing that c-Kit high expressing HSC exhibits a megakaryocytic lineage differentiation bias (Shin JY et al.) and megakaryocytic progenitors are enriched in CD34-CD38-/low cells (Steevels T et al.), these experiments show that briquilimab may skew HSC differentiation bias towards the megakaryocytic lineage.

Example 9

PHASE 1B/2A, DOSE ESCALATION STUDY OF PHARMACOKINETIC/PHARMACODYNAMIC AND PRELIMINARY CLINICAL ACTIVITY OF BRIQUILIMAB IN ADULT PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA (CSU) WHO REMAIN SYMPTOMATIC DESPITE TREATMENT WITH, OR WHO CANNOT TOLERATE, OMALIZUMAB

[0362] A randomized phase 1b/2a, multiple ascending dose trial divided into three distinct Parts was conducted to demonstrate the safety, tolerability, and efficacy of different dose levels of briquilimab in adult participants with CSU, who remain symptomatic despite treatment with H1-antihistamines and/or omalizumab or who cannot tolerate omalizumab. The trial explores up to seven ascending dose levels (Cohorts 1, 2, 3, 4b, 4a, 5, 5b, 6 and 7) as shown in FIGs. 1

and 2. Biquilimab is administered subcutaneously. Biquilimab consists of 50 mg/mL active ingredient in a solution containing sodium acetate anhydrous, sucrose, polysorbate 20, and water for injection. Placebo consists of inactive solution containing sodium acetate anhydrous, sucrose, polysorbate 20, and water for injection.

[0363] Biquilimab (formerly AMG 191 or JSP191) is a full-length humanized aglycosylated immunoglobulin G1 (IgG1) directed against human c-Kit, also known as CD117, expressed on the surface of a variety of normal cell types including MCs, hematopoietic stem cells and progenitors, melanocytes, germ cells and interstitial cells of Cajal (Lammie 1994). Biquilimab binding to c-Kit inhibits the binding of the ligand stem cell factor (SCF). In mast cells (MCs), activated KIT potentiates degranulation and regulates MC growth, differentiation, survival and chemotaxis (Gilfillan 2011). In vivo pharmacodynamic studies in non-human primates showed that biquilimab depletes injury-activated skin mast cells and basal mast cells in skin, lung, and colon, all of which, with time, were reversible. Inhibition of SCF signaling through c-Kit on mast cells leads to their apoptosis. Following depletion, tissue mast cells likely take more than 8 weeks to be replenished through differentiation from hematopoietic stem cells.

[0364] The trial is divided into three Parts (conducted in series) as follows:

Part 1 (Cohorts 1 and 2)

Open label dose cohorts

- Screening Period: 28 days (4 weeks)
- Treatment Period: 20 weeks
 - Cohort 1 (n = 3 to 6): Participants received 10 mg biquilimab at Week 0, 4, 12 and 20.
 - Cohort 2 (n = 3 to 6): Participants received 40 mg biquilimab at Week 0, 4, 12 and 20.

Part 2 (Cohorts 3, 4b, 4a, 5 and 5b)

Randomized, double-blind, placebo-controlled cohorts

- Screening Period: 28 days (4 weeks)
- Treatment Period: 24 weeks
 - Cohort 3 (n = 8): Participants are randomized in a 3:1 ratio to receive 80 mg biquilimab or placebo at 8-week intervals (Week 0, 8, 16, and 24).
 - Cohort 4 (n = 12): Participants are randomized in a 2:1 ratio to receive 120 mg biquilimab or placebo during the Treatment Period. The first 6 participants will enter Cohort 4a and be treated at 12-week intervals (Week 0, 12, and 24). The next 6

participants will enter Cohort 4b and be treated at 8-week intervals (Week 0, 8, 16, and 24).

- Cohort 5 (n = 8): Participants are randomized in a 3:1 ratio to receive 180 mg briquilimab or placebo at 12-week intervals (Week 0, 12 and 24).
- Cohort 5b (n = 8): Participants are randomized in a 3:1 ratio to receive 180 mg briquilimab or placebo once every 8 weeks (Q8W) (Weeks 0, 8, 16, and 24).

Part 3 (Cohorts 6 and 7)

Randomized, double-blind, placebo-controlled dose cohort

- Screening Period: 28 days (4 weeks)
- Treatment Period: 12 weeks
 - Cohort 6 (n = 4): Participants are randomized in a 3:1 ratio to receive a single dose of 240 mg briquilimab or placebo at Week 0.
 - Cohort 7 (n = 4): Participants are randomized in a 3:1 ratio to receive a single dose of 360 mg briquilimab or placebo at Week 0.

[0365] Participants in the randomized cohorts in Parts 2 and 3 will remain blinded to the identity of their treatment assignment until completion of the trial.

[0366] Patients include males and females, ≥ 18 years old with a diagnosis of symptomatic CSU despite treatment as defined by:

- a. diagnosis of CSU t for ≥ 6 months
- b. the presence of itch and hives for ≥ 8 consecutive weeks at any time prior to Screening despite current use of H1-antihistamines (as reported by the participant)
- c. The presence of itch and hives for ≥ 8 consecutive weeks at any time prior to Screening despite treatment with omalizumab or intolerance to omalizumab (as reported by the participant); and
- d. UAS7 of ≥ 16 and ISS7 of ≥ 8 on Days -10 through Day -3 of Screening, and with use of H1-antihistamines on stable dose up to 4-fold of the approved dose.

Duration of treatment:

Part 1

Duration of the trial (per participant): Screening Period (4 weeks), Treatment Period (20 weeks) and Safety Follow-up Period (24 weeks), approximately 48 weeks.

Part 2

Duration of the trial (per participant): Screening Period (4 weeks), Treatment Period (24 weeks) and Safety Follow-up Period (24 weeks), approximately 52 weeks.

Part 3

During the Treatment Period, participants will either receive one dose of placebo or briquilimab 240 mg SC (Cohort 6) at Week 0.

Duration of the trial (per participant): Screening Period (4 weeks), Treatment Period (12 weeks) and Safety Follow-up Period (24 weeks), is approximately 40 weeks.

Safety:

[0367] Safety is assessed by regularly performed laboratory testing (hematology, clinical chemistry, urinalysis), physical examinations, vital signs, ECG, taste change test, hair color change tests and by monitoring and evaluating adverse events (AEs) and treatment emergent adverse events (TEAEs) from signing the informed consent form through the end of treatment visit.

Efficacy:

[0368] Efficacy was measured via the Urticaria Activity Score (UAS7), as the sum of the Hives Severity Score (HSS7) and Itch Severity Score (ISS7), which is completed daily, and the Urticaria Control Test (UCT) completed periodically by the participants. The main efficacy analyses are based on the absolute and relative change from baseline scores of UAS7, ISS7, HSS7, and UCT at Week 12. The scores at other timepoints are also analyzed.

[0369] The UAS7 was assessed by the participant by completing the HSS and ISS daily.

[0370] The UAS7 is the sum of the daily hives severity score (HSS) score and the daily itch severity score (ISS) score for seven consecutive days. The possible range of the weekly UAS7 score is 0 – 42 with higher values indicating higher disease severity (Hollis et al. 2018; Mathias et al. 2015). Complete UAS7 response is defined as $UAS7 \leq 6$ or a reduction by 90%. The minimal important difference was defined as 9.5 to 10.5 points (Mathias et al. 2015).

[0371] The wheals (hives) severity score (HSS), defined by number of hives, was recorded by the participant daily, on a scale of 0 (none) to 3 (intense/severe) (see Table 1). A weekly score (HSS7) was derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is 0 – 21 with higher values indicating greater hives severity (Hawro et al. 2018). Complete hives response is defined as $HSS7 = 0$, the minimal important difference was defined as 5 to 5.5 points (Mathias et al. 2015).

Table 1. Scoring of Hives Severity Score

Score	Wheal (Hives)
0	None
1	Mild (1-20 hives/24 hours)

2	Moderate (21-50 hives/24 hours)
3	Severe (>51 hives/24hours)

[0372] The severity of the itch (ISS) was recorded by the participant twice daily, on a scale of 0 (none) to 3 (intense/severe) (see Table 2). A weekly score (ISS7) was derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is 0 – 21 with higher values indicating higher itch severity (Hawro et al. 2018). Complete itch response is defined as ISS7 = 0. The minimal important difference was defined as 4.5 to 5.0 points (Mathias et al. 2015).

Table 2. Scoring of Itch Severity Score

Score	Wheal (Hives)
0	None
1	Mild (minimal awareness; easily tolerated)
2	Moderate (definite awareness; bothersome but tolerable)
3	Severe difficult to tolerate)

[0373] Complete response rate: Proportion of participants who are urticaria free based on UAS7 = 0. Well-controlled rate: Proportion of participants who are well controlled based on UAS7 ≤ 6 or UCT ≥ 12.

[0374] Participants complete the UCT periodically. The UCT is a disease-specific measure consisting of four questions that retrospectively assesses participants' burden of disease over the previous 4 weeks. Disease control is a major treatment aim in CSU, and the UCT was specifically developed and validated to measure this in all forms of CU (Weller 2014). Concepts covered include disease activity, QOL survey, disease control, and therapy. Each of the four questions are scored on a scale of 0 to 4 (see Fig. 3). The UCT score is derived by adding up the scores from each of the four questions. A total score from 0 (no control) to 16 points (complete control) is derived, with a score of ≥ 12 indicating well-controlled disease. The UCT has high levels of validity and reliability, and accurately identifies participants with insufficiently controlled disease. Its minimal clinically important difference (MCID) is 3 points (Kulthanan 2016, Ohanyan 2017).

[0375] The primary efficacy analysis will be based on the modified intention to treat (mITT) analysis set.

[0376] For the UAS7, HSS7, ISS7 and UCT scores, change from baseline at Week 12 are summarized by cohort and by cohort and arm if the cohort is randomized. Point estimates and

95% confidence intervals will be presented. For between group comparisons in the randomized cohorts, statistical test of the change from baseline values at Week 12 based on ANCOVA (analysis of covariance) adjusting for the baseline UAS7, HSS7 and ISS7 scores, respectively, or an appropriate nonparametric test may be performed. Similar analyses is performed for the change from baseline at other times such as weeks 4 and 8. In addition to the change from baseline, percent change from baseline will be summarized.

[0377] The proportion of participants who are urticaria free based on UAS7=0 or are well controlled based on UCT $\geq$ 12 and based on UAS7 $\leq$ 6, respectively, is summarized at each time point (e.g., weeks 4, 8, 12). Additional summaries based on more detailed categorization of the UAS7 score are also provided. The categories are defined as follows: urticaria-free=0; well-controlled urticaria=1–6; mild =7–15; moderate =16–27; and severe urticaria=28–42.

[0378] Time to reach urticaria-free (UAS7=0), well-controlled urticaria based on UAS7 $\leq$ 6 and based on UCT $\geq$ 12 is analyzed separately using the Kaplan-Meier method. Descriptive summaries are provided for participants who reach the criteria for each endpoint.

[0379] For participants who have achieved well-controlled urticaria based on UAS7 $\leq$ 6, time to relapse, defined as UAS7 $\geq$ 12, is estimated using the Kaplan-Meier method.

[0380] Similar analyses are performed for the HSS7 and ISS7 scores as those proposed for the UAS7. Relevant thresholds are used to define the endpoints for each scale respectively.

[0381] Sensitivity analyses addressing imputation of potential missing data and modelling repeated measures using mixed effect models may be considered and additional details provided in the statistical analysis plan.

Pharmacokinetics:

[0382] Whole blood samples are collected for analysis of serum concentrations of briquilimab by a validated assay. PK parameters for briquilimab will be estimated following SC administration by non-compartmental method. The PK blood sampling is performed at specific PK-Sampling visits during the first days after first dose of IP and at follow-up visits in accordance with the Schedule of Assessments. Briquilimab pharmacokinetic parameters are estimated by non-compartmental method. Briquilimab pharmacokinetic parameter estimates include peak concentrations (C_{max}), time to reach C_{max} (t_{max}) and area under the concentration-time curve from dosing time to last quantifiable concentration (AUC_{last}). If data permit, additional applicable parameters are estimated. Briquilimab serum concentrations and pharmacokinetic parameters are summarized using descriptive statistics.

Pharmacodynamics:

[0383] Serum tryptase, anti-drug antibody blood sampling, and skin prick test with codeine are performed at Baseline (prior to first dosing), and at follow-up visits in accordance with the Schedule of Assessments. Skin biopsies (voluntary; for participants willing to participate, only) are performed at Baseline, Week 4, and Week 12. Pharmacodynamic data and ADA data is summarized using descriptive statistics.

Results:

[0384] Targeting mast cells with briquilimab is expected to provide clinical benefit in CSU by decreasing the number and activity of mast cells. Briquilimab is expected to reduce mast cell density wheal responses in CSU participants. This is evaluated, e.g., through changes from baseline in participant reported clinical outcome measures, skin biopsies, and serum tryptase levels.

[0385] Results indicated that targeting mast cells with briquilimab provided clinical benefit in CSU. Briquilimab was administered to patients at Day 0, Week 4, Week 12 and Week 20. Three patients were administered 10 mg of briquilimab, and three patients were administered 40 mg of briquilimab. Administration of 10 mg of briquilimab (subcutaneously) to patients with CSU did not appear to be efficacious at each dosing timepoint. However, administration of 40 mg of briquilimab to patients with CSU did appear to be efficacious at after dosing. A complete response was seen in one patient treated with 40 mg of briquilimab (subcutaneously) by Week 2, and a durable response was observed prior to the next dose at Week 4. Repeated dose administration (per protocol) resulted in meaningful reductions in UAS-7. A second patient with more severe disease at baseline treated with 40 mg of briquilimab (subcutaneously) showed improvements in UAS-7 on first and second doses. A third patient treated with 40 mg of briquilimab (subcutaneously) saw early reduction in UAS-7 after the first dose.

Example 10

PHASE 1B/2A, DOSE ESCALATION STUDY OF SAFETY,
PHARMACOKINETIC/PHARMACODYNAMIC AND PRELIMINARY CLINICAL ACTIVITY OF
BRIQUILIMAB IN ADULT PATIENTS WITH CHRONIC INDUCIBLE URTICARIA (CINDU) WHO
REMAIN SYMPTOMATIC DESPITE TREATMENT WITH H1-ANTIHISTAMINES

[0386] A randomized phase 1b/2a, multiple ascending dose trial divided into three distinct Parts was conducted to demonstrate the safety, tolerability, and efficacy of briquilimab in participants with Cold urticaria (ColdU) or Symptomatic Dermographism (SD), who remain symptomatic despite the use of H1-antihistamines. The trial explores three ascending dose

levels that are tested in three sequential cohorts. Briquilimab was administered subcutaneously. Briquilimab consisted of 50 mg/mL active ingredient in a solution containing sodium acetate anhydrous, sucrose, polysorbate 20, and water for injection. Placebo consisted of inactive solution containing sodium acetate anhydrous, sucrose, polysorbate 20, and water for injection.

[0387] Briquilimab (formerly AMG 191 or JSP191) is a full-length humanized aglycosylated immunoglobulin G1 (IgG1) directed against human c-Kit, also known as CD117, expressed on the surface of a variety of normal cell types including MCs, hematopoietic stem cells and progenitors, melanocytes, germ cells and interstitial cells of Cajal (Lammie 1994). Briquilimab binding to c-Kit inhibits the binding of the ligand stem cell factor (SCF). In mast cells (MCs), activated KIT potentiates degranulation and regulates MC growth, differentiation, survival and chemotaxis (Gilfillan 2011). In vivo pharmacodynamic studies in non-human primates showed that briquilimab depletes injury-activated skin mast cells and basal mast cells in skin, lung, and colon, all of which, with time, were reversible. Inhibition of SCF signaling through c-Kit on mast cells leads to their apoptosis. Following depletion, tissue mast cells likely take more than 8 weeks to be replenished through differentiation from hematopoietic stem cells.

[0388] In each cohort, the trial was divided into three periods as follows and shown in FIG. 28:

- Screening Period: up to two weeks
 - Treatment Period: twelve weeks
 - Cohort 1 (n = 3 to 6): Participants receive 40 mg briquilimab subcutaneously (SC) on Day 1 (Baseline).
 - Cohort 2 (n = 12): Participants receive 120 mg briquilimab SC at Day 1 (Baseline).
 - Cohort 3 (n = 12): Participants receive 180 mg briquilimab SC at Day 1 (Baseline).
- Through at least week 12 of the trial, participants should maintain stable doses of their urticaria concomitant medication as per standard of care (pre-screening therapy with H1 antihistamines at approved or increased doses up to four-fold).

[0389] Patients included males and females, ≥ 18 years old with a diagnosis of ColdU or SD for ≥ 3 months despite the use of H1-antihistamines as defined by:

- a. Diagnosis of ColdU or SD for ≥ 3 months, symptoms must comprise both wheal and itch or painful sensation;
- b. The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to Screening despite current use of H1-antihistamines (as reported by the participant) ;

- c. ColdU participants must have a positive cold stimulation test above 4°C using TempTest® (wheal and itch or painful sensation) on site during screening using TempTest® to be eligible; and
 - d. SD participants must have a positive FricTests® with 3 pins (wheal and itch) on site during Screening to be eligible,
- and with use of H1-antihistamines on stable dose up to 4-fold of the approved dose.

Duration of treatment:

[0390] Participants were treated once with either 40 mg (Cohort 1), 120 mg (Cohort 2), or 180 mg (Cohort 3) briquilimab. The trial was open-label.

Safety:

[0391] Safety was assessed by regularly performed laboratory testing (hematology, clinical chemistry, urinalysis), physical examinations, vital signs, ECG, taste change test, hair color change tests and by monitoring and evaluating adverse events (AEs) and treatment emergent adverse events (TEAEs) from signing the informed consent form through the end of treatment visit.

Efficacy:

[0392] Provocation tests were performed for evaluation of eligibility criteria (confirmation of ColdU and SD) and to assess the critical thresholds at visits. Efficacy was measured via provocation testing (TempTest® for ColdU and FricTest® for SD) performed on site and via the Urticaria Control Test (UCT) which was completed by the participants per guidance. Testing was carried out at skin sites that were not affected by urticaria in the last 24 hours. Usually, provocation testing, in positive participants, results in the rapid development of urticarial reactions. Wheals usually develop within minutes after provocation. (Magerl et al. 2016).

[0393] The provocation test for ColdU was the TempTest®. The TempTest® is an electronic testing device consisting of metallic cooling elements that can maintain a precise pre-set temperature from 4°- 44° C, applied to the skin. The participants place the inner forearm on an aluminum stencil on the device for 5 minutes. The stencil shows the temperature range continuously. After 10 minutes, the wheals appearing on the arm are compared to the stencil and the threshold temperature, where wheals are triggered, is recorded in °C. The critical temperature threshold (CTT) is the highest temperature sufficient to induce a positive test reaction (development of wheals). A positive provocation test at Screening is defined as wheal and itch or painful sensation at 4°C or higher.

[0394] The provocation test for SD was the FricTest® (Mlynek et al. 2013). FricTest® is a comb-like instrument with four tips of different lengths which allows for simultaneous dermal stimulation in four different provocation levels, from I (the weakest) to IV (the strongest). To obtain a response, FricTest® is placed vertically so that the four tips are touching the skin, and then stroked once with moderate pressure across the width of the volar surface of the forearm (or the patient's back) for a distance of approximately 6 centimeters. A positive response is defined by a palpable wheal of ≥ 3 mm in width (the diameter of FricTest® tips) at 10 min after provocation. Positive responses were documented for all provocation levels at which they occurred. If all four provocation levels induced wheals, the reaction was considered severe. The critical friction threshold (CFT) is the weakest provocation level sufficient to induce a positive test reaction. A positive provocation test at Screening was defined as a positive test response (wheal and itch or painful sensation) to provocation with the longest FricTest® tip provocation (level IV) which confirms the presence of SD.

Pharmacokinetics:

[0395] Whole blood samples were collected for analysis of serum concentrations of briquilimab by a validated assay. PK parameters for briquilimab were estimated following SC administration by non-compartmental method. The PK blood sampling was performed in accordance with the Schedule of Assessments. Briquilimab pharmacokinetic parameters were estimated by non-compartmental method. Briquilimab pharmacokinetic parameter estimates included peak concentrations (C_{max}), time to reach C_{max} (t_{max}) and area under the concentration-time curve from dosing time to last quantifiable concentration (AUC_{last}). Additional applicable parameters may be estimated. Briquilimab serum concentrations and pharmacokinetic parameters were summarized using descriptive statistics.

Pharmacodynamics:

[0396] Serum tryptase, stem cell factor (SCF), and anti-drug antibodies (ADAs) were assessed at Baseline (prior to first dosing) and at subsequent visits in accordance with the Schedule of Assessments. Mast cell counts were measured in skin biopsies (optional) and mast cell changes in nasal/buccal swabs (optional).

Results:

[0397] Targeting mast cells with briquilimab is expected to provide clinical benefit in CIndU by decreasing the number and activity of mast cells. This is evaluated, e.g., through changes from baseline in participant reported clinical outcome measures, skin biopsies, and serum tryptase levels.

[0398] Results indicated that targeting mast cells with briquilimab provided clinical benefit in ColdU and SD. Three patients were dosed at 40 mg of briquilimab subcutaneously (two patients with SD and one patient with ColdU). One of the two SD patients dosed at 40 mg showed a complete response. Twelve patients were dosed at 120 mg of briquilimab subcutaneously (eight with SD and four with ColdU). Seven of the SD patients and 3 of the ColdU patients dosed at 120 mg showed complete responses. For patients dosed at 120 mg, five of the eight patients with SD and three of the four patients with ColdU exhibited clinical response by day 15, and six of the eight patients with SD and three of the four patients with ColdU exhibited clinical response by day 29.

Example 11

COMPARISON OF PK PROFILES OF BRIQUILIMAB AND BARZOLVOLIMAB

[0399] Briquilimab (JSP191) is an anti-c-Kit antibody under clinical development. A benchmark anti-c-Kit antibody is barzolvolimab (CDX-0159) being developed by Celldex Therapeutics, Inc. This example compares the pharmacokinetic profiles of briquilimab (JSP191) and barzolvolimab (CDX-0159) in humans.

[0400] The serum concentrations of briquilimab following intravenous (IV) injections in patients in a clinical trial for severe combined immunodeficiency (SCID) were plotted against the drug doses (FIG. 26A). A reported PK chart for barzolvolimab (IV) among healthy volunteers is included as FIG. 26B for comparison. The PK profile of briquilimab following subcutaneous (SC) injections was likewise created (FIG. 27A), compared to that of barzolvolimab (FIG. 27B). In both cases, at similar doses, briquilimab's exposure declined more quickly than barzolvolimab.

[0401] Inhibition of c-Kit signaling can lead to organized cell death and phagocytic clearance of mast cells. On the one hand, however, the blockade needs to be higher than a threshold level to deplete the mast cells, as partial c-Kit inhibition can only inhibit mast cell activation. On the other hand, sustained c-Kit blockade can result in undesirable effects on other c-Kit-expressing cells. Such a tension, therefore, presents a significant challenge for developing c-Kit antibodies for treating mast cell-mediated diseases and disorders.

[0402] In an unexpected discovery, briquilimab exhibited more rapid pharmacokinetic clearance as compared to barzolvolimab (FIGs. 26A, 26B, 27A and 27B); the shortened drug exposure, however, was still sufficient for mast cell depletion which occurred rather quickly as well. Such improved clearance, therefore, presents a unique advantage for

briquilimab as it can help minimize adverse effects on other, non-targeted, c-Kit-positive cells.

[0403] Yet another advantage of briquilimab is that it can be more potent than barzolvolimab, at least at lower doses. While the clinical dose of barzolvolimab for treating chronic urticaria is 3 mg/kg (Terhorst-Malawi *et al.*, *Allergy*. 2023;78:1269-1279), briquilimab exhibited potent and lasting efficacy at doses as low as about 1 mg/kg.

[0404] Activation of the c-Kit upon binding by stem cell factor (SCF) leads to dimerization, autophosphorylation and receptor internalization. The conventional antibody barzolvolimab inhibits c-Kit activity by inhibiting c-Kit dimerization. It has been shown, however, briquilimab blocks the interaction between c-Kit and SCF directly, whose receptor antagonism is accordingly likely more potent.

[0405] In accordance with one embodiment of the present disclosure, therefore, provided is a method for treating a mast cell-mediated disease or disorder in a subject in need thereof. In some embodiments, the method entails administering to the subject an effective amount of briquilimab or an antigen binding fragment thereof.

References

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2. Steevels T et al., Co-expression of the collagen receptors leukocyte-associated immunoglobulin-like receptor-1 and glycoprotein VI on a subset of megakaryoblasts. *Haematologica*, 2010; 95(12)
3. Blank U et al, Signaling pathways governing stem-cell fate. *Blood* 2007;10; 492-503.

* * *

[0406] The various embodiments described above can be combined to provide further embodiments. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, application and publications to provide yet further embodiments. It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims

and their equivalents. These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

[0407] All of the U.S. patents, U.S. patent application publications, U.S. patent application, foreign patents, foreign patent application and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entireties.

Claims

1. A method of treating, inhibiting, or preventing a mast cell-related disease or disorder in a human subject, comprising administering to the human subject an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), wherein the subject is administered:
 - a) two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody, and wherein each dose is administered between eight weeks to six months apart; or
 - b) one dose of the anti-c-kit IgG antibody, wherein the dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-Kit IgG antibody of the anti-c-Kit IgG antibody.
2. The method of claim 1, wherein each dose comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, or about 360 mg of the anti-c-kit IgG antibody.
3. The method of claim 2, wherein each dose comprises about 40 mg, about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of the anti-c-kit IgG antibody.
4. The method of any one of claims 1-3, wherein the disease or disorder is selected from the group consisting of: urticaria, chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU), chronic idiopathic urticaria (CIU), urticaria pigmentosa, prurigo nodularis, esophagitis (optionally, eosinophilic esophagitis), asthma, anaphylaxis, mastocytosis, mast

cell activation syndrome (MCAS), fibrosis, atherosclerosis, allergic diseases and disorders, dermatitis, endometriosis, interstitial cystitis, and inflammatory bowel disease.

5. The method of claim 4, wherein the disease or disorder is chronic spontaneous urticaria (CSU), optionally wherein the subject remains symptomatic despite treatment with an antihistamine, and the subject is administered two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody, and wherein each dose is administered between eight weeks to six months apart.

6. The method of claim 4, wherein the disease or disorder is chronic inducible urticaria (CIndU), optionally Cold urticaria (ColdU) or Symptomatic Dermographism (SD), and the subject is administered two or more doses of the anti-c-kit IgG antibody, wherein each dose comprises about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit antibody, and wherein each dose is administered between eight weeks to six months apart.

7. The method of any one of claims 1-6, wherein the anti-c-kit antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously.

8. The method of any one of claims 1-7, wherein the subject is administered two or more doses of the anti-c-kit IgG antibody, and wherein each of the doses is administered between about eight weeks and about six months apart, between about eight weeks to about four months apart, between about eight weeks to about twelve weeks apart, between about twelve

weeks to about six months apart, between about twelve weeks to about four months apart, about 8 weeks apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, or about six months apart, optionally wherein the time interval between each dose varies.

9. The method of any one of claims 1-8, wherein the method results in a $UAS7 \leq 6$ or a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90%.

10. The method of any one of claims 1-9, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

11. The method of claim 10, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

12. A method for selectively depleting mast cells as opposed to hematopoietic stem and progenitor cells (HSPCs) in a subject, the method comprising administering to the subject one or more therapeutically effective doses of an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), wherein each dose comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody.

13. The method of claim 12, wherein each dose comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, or about 360 mg of the anti-c-kit IgG antibody.

14. The method of claim 13, wherein each dose comprises about 40 mg, about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of the anti-c-kit IgG antibody.

15. The method of any one of claims 12-14, wherein the anti-c-kit IgG antibody is delivered to the subject systemically, optionally wherein the anti-c-kit antibody is delivered intravenously or subcutaneously.

16. The method of any one of claims 12-15, wherein the subject is administered two or more doses of the anti-c-kit antibody.

17. The method of claim 16, wherein each of the doses is administered between eight weeks to one year apart, between eight weeks to six months apart, between eight weeks to four months apart, between twelve weeks to one year apart, between twelve weeks to six months apart, between twelve weeks and four months apart, about 8 weeks apart, about 9 weeks apart, about 10 weeks apart, about 12 weeks apart, about four months apart, about six months apart, eight months apart, about ten months apart, or about one year apart, optionally wherein the time interval between each dose varies.

18. The method of any one of claims 12-17, wherein the method results in a reduction of mast cells of at least 50%, at least 70%, at least 70%, at least 80%, or at least 90% and a reduction in HSPCs of less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%.

19. The method of any one of claims 12-18, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

20. The method of claim 19, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

21. A kit comprising one or more doses of an anti-c-kit IgG antibody comprising heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and

VL CDR3 = QQNNEDPYT (SEQ ID NO: 11), wherein each of the one or more doses comprises about 20 mg to about 500 mg, optionally about 35 mg to about 350 mg or about 50 mg to about 300 mg, of the anti-c-kit IgG antibody.

22. The kit of claim 21, wherein each of the one or more doses comprises or consists of about 40 mg to about 360 mg, about 50 mg to about 300 mg, about 50 mg to about 280 mg, about 50 mg to about 240 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 340 mg, or about 360 mg of the anti-c-kit IgG antibody.

23. The kit of claim 22, wherein the kit comprises one or more doses comprising of about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of the anti-c-kit IgG antibody.

24. The kit of any one of claims 21-23, wherein the kit comprises two or more doses of the anti-c-kit IgG antibody.

25. The kit of claim 24, wherein each of the two or more doses of the anti-c-kit IgG antibody comprises about 80 mg, about 120 mg, about 180 mg, about 240 mg, or about 360 mg of the anti-c-kit antibody.

26. The kit of any one of claims 21-25, wherein the anti-c-kit IgG antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

27. The kit of claim 26, wherein the anti-c-kit IgG antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.

28. A method of altering the differentiation pathway of hematopoietic stem cells (HSCs) and/or hematopoietic stem and progenitor cells (HSPCs), comprising contacting the HSCs

and/or HSPCs with an anti-c-kit IgG antibody or antigen-binding fragment thereof, wherein the anti-c-kit antibody inhibits binding of stem cell factor (SCF) to c-kit on the cell surface.

29. The method of claim 28, wherein the method results in increased differentiation of the cells along the megakaryocytic lineage.

30. The method of claim 28 or claim 29, wherein the anti-c-kit antibody or antigen-binding fragment thereof comprises at least five CDRs selected from: heavy chain CDRs: VH CDR1 = YNMH (SEQ ID NO: 6); VH CDR2 = IYSGNGDTSYNQKFKG (SEQ ID NO: 7); and VH CDR3 = ERDTRFGN (SEQ ID NO: 8) and light chain CDRs: VL CDR1 = RASESVDIYGNSFMH (SEQ ID NO: 9); VL CDR2 = LASNLES (SEQ ID NO: 10); and VL CDR3 = QQNNEDPYT (SEQ ID NO: 11).

31. The method of any one of claims 28-30, wherein the anti-c-kit antibody comprises a variable heavy chain comprising SEQ ID NO: 4 and a variable light chain comprising SEQ ID NO: 5.

32. The method of claim 31, wherein the anti-c-kit antibody comprises a heavy chain comprising SEQ ID NO: 2 and a light chain comprising SEQ ID NO: 3.