

**METHOD OF TREATING AN AUTOIMMUNE DISEASE WITH ANTAGONISTIC
CD40 MONOCLONAL ANTIBODIES**

CROSS REFERENCE TO RELATED APPLICATIONS

- 5 **[0001]** This application claims benefit of U.S. Provisional Application No. 63/070,209, filed August 25, 2020, which is hereby incorporated in its entirety for all purposes.

SEQUENCE LISTING

- 10 **[0002]** The instant application contains a Sequence Listing that has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 22, 2021, is named 200896-0017-00-WO-000026_SL.txt and is 53,479 bytes in size.

FIELD

- 15 **[0003]** The disclosure provides methods of treating an autoimmune disease with antibodies that bind CD40 and do not exhibit CD40 agonist activity. The antibodies comprise a modified IgG1 Fc domain, and exhibit minimal activation of immature dendritic cells. Appropriate doses and administration regimens for the anti-CD40 antibodies are also provided.

BACKGROUND

- 20 **[0004]** CD40 is a co-stimulatory molecule belonging to the tumor necrosis factor (TNF) receptor superfamily that is present on antigen presenting cells (APC), including dendritic cells, B cells, and macrophages. APCs are activated when CD40 binds its ligand, CD154 (CD40L), on T_H cells. CD40-mediated APC activation is involved in a variety of immune responses, including cytokine production, up-regulation of co-stimulatory molecules
25 (such as CD86), and enhanced antigen presentation and B cell proliferation. CD40 can also be expressed by endothelial cells, smooth muscle cells, fibroblasts, and epithelial cells.

- 30 **[0005]** CD40 activation is also involved in a variety of undesired T cell responses related to autoimmunity, transplant rejection, or allergic responses, for example. One strategy for controlling undesirable T cell responses is to target CD40 with an antagonistic antibody. For example, monoclonal antibody HCD122 (Lucatumumab), formerly known as Chiron 1212, is currently in clinical trials for the treatment of certain CD40-mediated inflammatory

diseases. See “Study of HCD122 (Lucatumumab) and Bendamustine Combination Therapy in CD40⁺ Rituximab-Refractory Follicular Lymphoma,” Clinical Trials Feeds, on the Internet at hypertext transfer protocol: clinicaltrialsfeeds.org/clinical-trials/show/NCT01275209 (last updated January 11, 2011). Monoclonal antibodies, however, can display agonist activity.

- 5 For example, the usefulness of the anti-CD40 antibody, Chi220, is limited by its weak stimulatory potential. See Adams, et al., “Development of a chimeric anti-CD40 monoclonal antibody that synergizes with LEA29Y to prolong islet allograft survival,” *J. Immunol.* 174: 542-50 (2005).

SUMMARY

- 10 **[0006]** Provided is a method of treating an autoimmune disease in a human patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of the antibody polypeptide disclosed herein. In an embodiment, the autoimmune disease is Sjögren’s Syndrome.

- [0007]** The method comprises administering a monoclonal antibody directed against
15 an epitope of CD40 associated with antagonism. In an embodiment, the monoclonal antibody is BMS-986325. The disclosed antibodies potently inhibits CD40 signaling in B-cell proliferation driven both by soluble CD40L and cell-associated CD40L. Additionally, disclosed antibodies inhibit CD40L-induced signaling on DCs, resulting in reduced production of pro-inflammatory cytokines, and reduction of cell surface activation markers,
20 CD86 and CD54. The disclosed antibodies are fully cross-reactive with CD40 from cynomolgus monkey, and treatment of cynomolgus monkeys with disclosed antibodies leads to dose-dependent receptor engagement, reduction of CD40L-driven B-cell activation ex vivo and suppression of a T-cell-dependent antibody response (TDAR). Further, disclosed antibodies comprise a fragment crystallizable (Fc) region containing a mutation that reduces
25 or eliminates binding to Fc receptors, eliminating Fc gamma receptor (FcγR)-mediated cross-linking or clustering. Importantly, disclosed antibodies exhibit no evidence of CD40 agonism in either *in vitro* or *in vivo* preclinical testing.

- [0008]** The method is practiced by administering to the patient at least one dose of an isolated antibody, or antigen binding portion thereof, that specifically binds to human CD40,
30 wherein the antibody comprises a first polypeptide portion comprising a heavy chain variable region, and a second polypeptide portion comprising a light chain variable region, wherein:

the heavy chain variable region comprises (i) a CDR1 comprising SYWMH (SEQ ID NO: 1), a CDR2 comprising QINPTTGRSQYNEKFKT (SEQ ID NO: 2), and a CDR3 comprising WGLQPFAY (SEQ ID NO: 3); and

the light chain variable region comprises a CDR1 comprising KASQDVSTAVA (SEQ ID NO: 7), a CDR2 comprising SASYRYT (SEQ ID NO: 8), and a CDR3 comprising QQHYSTPWT (SEQ ID NO: 9),

wherein the dose is selected from 0.3 milligram (mg) to 1000 mg of the antibody, or antigen binding portion thereof.

[0009] In an embodiment, the method is practiced an isolated antibody or antigen binding portion thereof, wherein the antibody comprises a first polypeptide portion comprising a heavy chain variable region, and a second polypeptide portion comprising a light chain variable region, wherein:

the heavy chain variable region comprises the amino acid sequence of QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINP **TTGRSQYNEKFKT**TRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLOPFAYW GQGTLVTVSS (SEQ ID NO: 4), and

the light chain variable region comprises the amino acid sequence of DIQMTQSPSFLSASVGDRVITITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYT GVPSRFGSGSGTDFTLTISLQPEDFATYYCQQHYSTPWTFGGGTKVEIK (SEQ ID NO: 10).

[0010] In certain embodiments of the method, the isolated antibody or antigen binding portion thereof comprises the first polypeptide portion comprising a human heavy chain constant region; and the second polypeptide portion comprising a human light chain constant region. The isolated antibody or antigen binding portion thereof described herein comprises a human IgG1 Fc domain comprising a mutation at Kabat position 238 that reduces binding to Fc-gamma-receptors (FcγRs), wherein proline 238 (P238) is mutated to one of the residues selected from the group consisting of lysine, serine, alanine, arginine, and tryptophan, and wherein the antibody or antigen binding portion thereof has reduced FcγR binding. In an embodiment, the proline at Kabat position 238 is substituted with lysine.

[0011] The isolated antibody or antigen binding portion thereof described herein can comprise an Fc domain which comprises an amino acid sequence selected from:

EPKSCDKTHTCPPCPAPELLGGKSSVFLFPPKPKDTLMISRTPEVTCVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
5 NHYTQKSLSLSPG (SEQ ID NO: 13; IgG1-P238K (-C-term Lys)),

EPKSCDKTHTCPPCPAPELLGGKSSVFLFPPKPKDTLMISRTPEVTCVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
10 NHYTQKSLSLSPGK (SEQ ID NO: 14; IgG1-P238K),

*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELL
GGKSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAIEKTISKAKGQPRE
15 PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSG
DSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
15; CH1-IgG1-P238K (-C-term Lys)),*

*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPAPELL
20 LGGKSSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSG
DSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
16; CH1-IgG1-P238K),*

EPKSCDKTHTCPPCPAPELLGGKSSVFLFPPKPKDTLMISRTPEVTCVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSRDEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
25 NHYTQKSLSLSPG (SEQ ID NO: 17; IgG1f-P238K (-C-term Lys)),

EPKSCDKTHTCPPCPAPELLGGKSSVFLFPPKPKDTLMISRTPEVTCVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNAKALPAIEKTISKAKGQPREPQVYTLPPSRDEMTKNQVSLTCLVKGFYPSDIA
VEWESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALH
30

NHYTQKSLSLSPGK (SEQ ID NO: 18; IgG1f-P238K),

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEL
LGGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT
5 KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:
19; CH1-IgG1f-P238K (-C-term Lys)),

or

10 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAV
LQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKPKSCDKTHTCPPCPAPEL
LGGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
15 GSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK (SEQ ID No:
20; CH1-IgG1f-P238K).

[0012] The isolated antibody or antigen binding portion thereof can comprise a human IgG1 Fc domain comprising the amino acid sequence of SEQ ID NO: 13 or SEQ ID NO: 14.

20 **[0013]** In some embodiments, the method is practiced with an isolated antibody or antigen binding portion thereof described herein, wherein the first polypeptide portion comprises or consists of an amino acid sequence selected from the group consisting of:

QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQG
LEWMG**QINPTTGRSOYNEKFKTR**VTITADKSTSTAYMELSSLRSED TAVYYCAR
WGLOPFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
25 SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVK
KSCDKTHTCPPCPAPELGGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQK
30 SLSLSPG (SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K - no terminal lysine),

QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQG
LEWMG**QINPTTGRSOYNEKFKTR**VTITADKSTSTAYMELSSLRSED TAVYYCAR

WGLOPFAYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
 SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
 KSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 5 LPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
 GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
 SLSLSPGK (SEQ ID NO: 6; HC_Y12XX-hz28-CH1-IgG1-P238K - with terminal lysine),

QVQLVQSGAEVKKPGSSVKVCKASGYAFT**SYWMH**WVRQAPGQG
 LEWMG**QINPTTGRSOYNEKFKT**RVTTITADKSTSTAYMELSSLRSED TAVYYCAR
 10 **WGLOPFAY**WGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
 SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
 KSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 15 GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
 SLSLSPG (SEQ ID NO: 21; HC_Y12XX-hz28-CH1-IgG1f-P238K - no terminal lysine),
 and

QVQLVQSGAEVKKPGSSVKVCKASGYAFT**SYWMH**WVRQAPGQG
 LEWMG**QINPTTGRSOYNEKFKT**RVTTITADKSTSTAYMELSSLRSED TAVYYCAR
 20 **WGLOPFAY**WGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
 SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRV
 KSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
 FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA
 LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN
 25 GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
 SLSLSPGK (SEQ ID NO: 22; HC_Y12XX-hz28-CH1-IgG1f-P238K - with terminal
 lysine); and

the second polypeptide portion comprises or consists of the amino acid
 sequence of

30 DIQMTQSPSFLSASVGDRVTTITC**KASQDVSTAVA**WYQQKPGKAPKL
 LIY**SASYRYT**GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC**QOHYSTPWT**FGGGTK
 VEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV

TEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11; LC_Y12XX-hz28-CL).

[0014] In some embodiments, the method is practiced with the antibody or antigen binding portion thereof as described herein, wherein the first polypeptide portion comprises or consists of an amino acid sequence of

QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWM
GQINPTTGRSOYNEKFKTRVTTITADKSTSTAYMELSSLRSEDTAVYYCARWGLOP
FAYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
 LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT
 10 HTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
 DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
 KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
 YKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
 (SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K - no terminal lysine);

and

the second polypeptide portion comprises or consists of the amino acid sequence of
 DIQMTQSPSFLSASVGDRVTTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYT
 GVPSRFGSGSGTDFTLTISLQPEDFATYYCQQHYSTPWTFGGGTKVEIKRTVAAP
 SVFIFPPSDEQLKSGTASVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDY
 20 *SLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 11;
 LC_Y12XX-hz28-CL).

[0015] In some embodiments, the method is practiced with the antibody BMS-986325 wherein the first polypeptide portion has the amino acid sequence of

QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWM
 25 GQINPTTGRSOYNEKFKTRVTTITADKSTSTAYMELSSLRSEDTAVYYCARWGLOP
FAYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGA
 LTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT
 HTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
 DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
 30 KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
 YKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG
 (SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K - no terminal lysine); and

the second polypeptide portion has the amino acid sequence of
 DIQMTQSPSFLSASVGDRVITITCKASODVSTAVAWYQQKPGKAPKLLIYSSASYRYT
 GVPSRFGSGSGTDFTLTISLQPEDFATYYCQOHYSTPWTFGGGGTKVEIKRTVAAP
 SVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDSTY
 5 *SLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC* (SEQ ID NO: 11;
 LC_Y12XX-hz28-CL).

[0016] In the methods disclosed, the isolated antibody or antigen binding portion thereof described herein can be a chimeric antibody. The isolated antibody or antigen binding portion thereof described herein can be a humanized antibody. The isolated antibody or antigen binding portion thereof described herein can comprise a human heavy chain constant region and a human light chain constant region.

[0017] In the methods disclosed, the antibody or antigen binding portion thereof disclosed herein, is an antigen binding portion selected from the group consisting of Fv, Fab, F(ab')₂, Fab', dsFv, scFv, sc(Fv)₂, diabodies, and scFv-Fc. The isolated antibody or antigen binding portion thereof as described herein can be an scFv-Fc.

[0018] The antibody or antigen binding portion thereof disclosed herein can be linked to a therapeutic agent.

[0019] The antibody or antigen binding portion thereof disclosed herein can be linked to a second functional moiety having a different binding specificity than said antibody or antigen binding portion thereof.

[0020] The antibody or antigen binding portion thereof disclosed herein can further comprise an additional moiety.

[0021] Optionally, the antibody, or the antigen-binding portion thereof, is administered with an immunosuppressive/immunomodulatory and/or anti-inflammatory agent. Administration may be simultaneous or sequential. An exemplary agent is a CTLA4 mutant molecule, such as L104EA29Y-Ig (belatacept). In such a method of treating or preventing an autoimmune or inflammatory disease in a subject, the subject preferably has a disease selected from the group consisting of: Addison's disease, allergies, anaphylaxis, ankylosing spondylitis, asthma, atherosclerosis, atopic allergy, autoimmune diseases of the ear, autoimmune diseases of the eye, autoimmune hepatitis, autoimmune parotitis, bronchial asthma, coronary heart disease, Crohn's disease, diabetes, epididymitis, glomerulonephritis,

Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hemolytic anemia, idiopathic thrombocytopenic purpura, inflammatory bowel disease, immune response to recombinant drug products (e.g., Factor VII in hemophiliacs), lupus nephritis, lupus nephritis, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, pemphigus, psoriasis, 5 rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren's syndrome, spondyloarthropathies, thyroiditis, transplant rejection, vasculitis, and ulcerative colitis.

[0022] Also contemplated is an antibody, or antigen binding portion thereof as disclosed herein, for use as a medicament for an autoimmune disease, such as Sjögren's syndrome. Further contemplated is an antibody, or antigen binding portion thereof as disclosed here, or a medicament comprising the same, for use to treat a subject in need thereof, 10 for instance a subject diagnosed with Sjögren's syndrome. Further contemplated is an antibody, or antigen binding portion thereof as disclosed herein in a therapeutically-effective amount, for use in treating or preventing an autoimmune disease such as Sjögren's syndrome, wherein the antibody or antigen binding portion thereof is for administering to a patient in 15 need thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0023] Figure 1 depicts the amino acid sequences of the heavy chain and the light chain of BMS-986325.

[0024] Figures 2A-2C depicts a summary of in vitro primary pharmacodynamics data 20 for BMS-986325. Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CD40L, CD40 ligand; CDC, complement dependent cytotoxicity; CHO, Chinese hamster ovary; DCs, dendritic cells; EC50, concentration required for 50% maximal effect; FcγR, Fc gamma receptor; IC50, concentration at which 50% inhibition observed; iDC, monocyte-derived dendritic cells; 25 IgG1, immunoglobulin G1; IL, interleukin; Kd, dissociation constant; NA, not available; NK, natural killer cells; SPR, surface plasmon resonance.

[0025] Figure 3 depicts a summary of in vivo primary pharmacodynamics data for BMS-986325. Abbreviations: CD40L, CD40 ligand; F, female; KLH, keyhole limpet hemocyanin; M, male; NA, not available; PD, pharmacodynamics; RO, receptor occupancy; 30 SC, subcutaneous.

[0026] Figure 4 depicts a SAD dose escalation scheme and the corresponding projected safety and efficacy margins of BMS-986325 for SAD intravenous doses. Abbreviations: AUC(INF), area under the concentration-time curve from time zero to infinity; Cmax, maximum observed concentration; IV, intravenous; MABEL, minimum anticipated biological effect level; NOAEL, no-observed-adverse-effect level; RO, receptor occupancy; RO, receptor occupancy; SAD, single-ascending dose.

[0027] Figure 5 depicts safety margins for BMS-986325 calculated from a 1-month GLP-toxicology study in monkeys. Abbreviations: AUC, area under the concentration-time curve; Cmax, maximum observed concentration; FIH, first-in-human; GLP Good Laboratory Practice; INF, infinity; IV, intravenous; NOAEL, no observed adverse effect (dose) level; SAD, single-ascending dose; SC, subcutaneous; qw, once weekly.

DETAILED DESCRIPTION

[0028] The present disclosure is directed to a method of treating an autoimmune disease such as Sjögren's Syndrome in a human patient by administration of antagonistic anti-CD40 antibodies. For therapeutic targets such as CD40, FcγR-mediated cross-linking of anti-CD40 antibodies has the potential to lead to undesirable agonist signaling and potential for toxicity. The methods of the present disclosure administer an antagonistic anti-CD40 antibody having reduced engagement of the "low affinity" FcγRs: hCD32a/FcγRIIa, hCD32b/FcγRIIb, and hCD16a/FcγRIIIa, as well as reduced engagement to "high affinity" FcγR hCD64. Reduced engagement of low affinity FcγRs is expected to reduce the likelihood of undesirable agonist signaling and undesirable potential for toxicity.

Definitions & Abbreviations

[0029] Further abbreviations and definitions are provided below.

	APC	antigen presenting cells
25	CD54	also referred to as ICAM-1
	CDR	complementarity determining regions
	C _H or CH	constant heavy chain
	C _L or CL	constant light chain
	CHO cell	Chinese hamster ovary cell
30	dAb	domain antibody
	DC	dendritic cell

	DTPA	diethylenetriaminepentaacetic acid
	FcγR	interchangeable with FcγR
	FcγR	Fc-gamma-receptor
	FR	Framework region
5	GM-CSF	granulocyte macrophage colony stimulating factor
	HC	heavy chain
	ICAM-1	intracellular adhesion molecule 1
	iDC	immature dendritic cells
	IFN	interferon
10	IgG	immunoglobulin G
	IL-6	interleukin-6
	LC	light chain
	mAb	monoclonal antibody
	mg	milligram
15	ml or mL	milliliter
	ng	nanogram
	nM	nanomolar
	Pentetic acid	diethylenetriaminepentaacetic acid
	PD	pharmacodynamics
20	pI	isoelectric point
	PK	pharmacokinetics
	q2wk	once every two weeks
	qwk	once a week
	SPR	surface plasmon resonance
25	TDAR	T-cell-dependent antibody response
	TNF	tumor necrosis factor
	μg	microgram
	μM	micromolar
	V _L or VL	variable light chain domain
30	V _k or VK	kappa variable light chain domain
	V _H or VH	variable heavy chain domain

[0030] In accordance with this detailed description, the following abbreviations and definitions apply. It must be noted that as used herein, the singular forms “a”, “an”, and “the”

include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an antibody” includes a plurality of such antibodies and reference to “the dosage” includes reference to one or more dosages and equivalents thereof known to those skilled in the art, and so forth.

5 [0031] As used here, the term “about” is understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. Generally, “about” encompasses a range of values that are plus/minus 10% of a referenced value unless indicated otherwise in the specification.

[0032] It is understood that any and all whole or partial integers between the ranges
10 set forth are included herein.

[0033] CD40 is also known and referred to as B-cell surface antigen CD40, Bp50, CD40L receptor, CDw40, CDW40, MGC9013, p50, TNFRSF5, and Tumor necrosis factor receptor superfamily member 5. “Human CD40” refers to the CD40 comprising the following amino acid sequence:

15 MVRLPLQCVL WGCLLTAVHP EPPTACREKQ YLINSQCCSL CQPGQKLVSD
CTEFTETECL PCGESEFLDT WNRETHCHQH KYCDPNLGLR VQQKGTSETD
TICTCEEGWH CTSEACESCV LHRSCSPGFG VKQIATGVSD TICEPCPVGF
FSNVSSAFEK CHPWTSCETK DLVVQQAGTN KTDVVCGPQD RLRALVVIPI
IFGILFAILL VLVFIKKVAK KPTNKAPHPK QEPQEINFPD DLPGSNTAAP
20 VQETLHGCP VTQEDGKESR ISVQERQ (SEQ ID NO: 12).

[0034] As used herein, the term “variable domain” refers to immunoglobulin variable domains defined by Kabat et al., Sequences of Immunological Interest, 5th ed., U.S. Dept. Health & Human Services, Washington, D.C. (1991). The numbering and positioning of CDR amino acid residues within the variable domains is in accordance with the well-known
25 Kabat numbering convention. VH, “variable heavy chain” and “variable heavy chain domain” refer to the variable domain of a heavy chain. VL, “variable light chain” and “variable light chain domain” refer to the variable domain of a light chain.

[0035] The term “human,” when applied to antibodies, means that the antibody has a sequence, e.g., FR and/or CH domains, derived from a human immunoglobulin. A sequence
30 is “derived from” a human immunoglobulin coding sequence when the sequence is either: (a) isolated from a human individual or from a cell or cell line from a human individual; (b)

isolated from a library of cloned human antibody gene sequences or of human antibody variable domain sequences; or (c) diversified by mutation and selection from one or more of the polypeptides above.

[0036] An “isolated” compound as used herein means that the compound is removed from at least one component with which the compound is naturally associated with in nature.

[0037] The anti-CD40 antibody of the present disclosure comprise a variable heavy chain and a variable light chain, each of which contains three complementarity-determining regions (CDRs) and four framework regions (FRs), arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The CDRs contain most of the residues that form specific interactions with the antigen and are primarily responsible for antigen recognition.

[0038] The methods of the present disclosure administer an anti-CD40 antibody comprising CDRs of humanized antibody Y12XX-hz28 (Vh-hz14; Vk-hz2) and a human IgG1 Fc domain comprising a mutation at Kabat position 238 that reduces binding to Fc-gamma-receptors (FcγRs). *See* US Publication No. 2020-0157233. An overview of the amino acid sequences of the heavy chain variable region and light chain variable region is provided in Table 1. The table includes a short hand name and a more detailed name for each amino acid sequence, as well as the sequence identifiers.

Table 1

Antibody	HC Variable Region	LC Variable Region
Y12XX-hz28	Vh-hz14	Vk-hz2
	QVQLVQSGAEVKKPGSSVKV SCKASGYAFTSYWMHWVRQ APGQGLEWMGQINPTTGRSQ YNEKFKTRVTITADKSTSTAY MELSSLRSEDVAVYYCARWG LQPFAYWGQGLTVTVSS (SEQ ID NO: 4)	DIQMTQSPSFLSASVGDRV ITCKASQDVSTAVAWYQQ KPGKAPKLLIYSASYRYTG VPSRFGSGSGTDFLTISL QPEDFATYYCQQHYSTPWT FGGGTKVEIK (SEQ ID NO: 10)

[0039] In a specific embodiment, the anti-CD40 antibodies of the present disclosure comprises the CDRs of humanized antibody Y12XX-hz28 (Vh-hz14; Vk-hz2). Details of the amino acid sequences of Y12XX-hz28 are provided in Table 2.

Table 2

Y12XX-hz28 sequences (Vh-hz14; Vk-hz2)

Heavy chain variable region	QVQLVQSGAEVKKPGSSSVKVSCKASGYAFT <u>S</u> <u>YWMH</u> WVRQAPGQGLEWMG <u>QINPTTGRSQYNE</u> <u>KFKT</u> RVTTITADKSTSTAYMELSSLRSED ~~TAV~~ YYCAR <u>WGLQPFAY</u> WGQGT ~~LVTVSS~~ SEQ ID NO: 4)	Vh-hz14 (SEQ ID NO: 4; CDRs underlined)
VH-CDR1	SYWMH SEQ ID NO: 1)	Amino acids 31-35 of SEQ ID NO: 4
VH-CDR2	QINPTTGRSQYNEKFKT (SEQ ID NO: 2)	Amino acids 50-66 of SEQ ID NO: 4
VH-CDR3	WGLQPFAY (SEQ ID NO: 3)	Amino acids 99-106 of SEQ ID NO: 4
HC_Y12XX-hz28-CH1-IgG1-P238K (is IgG1 with and without C-terminal lysine)	QVQLVQSGAEVKKPGSSSVKVSCKASGYAFT <u>S</u> <u>YWMH</u> WVRQAPGQGLEWMG <u>QINPTTGRSQYNE</u> <u>KFKT</u> RVTTITADKSTSTAYMELSSLRSED ~~TAV~~ YYCAR <u>WGLQPFAY</u> WGQGT ~~LVTVSS~~ ASTKGPS VFPLAPSSKSTSGGTAAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPSSSLGTQTYICNVNHKPSNTKVDKRV KSCDKTHTCPPCPAPELLGGKSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGS FFLYSKLTVDKSRWQQGNVFS ~~CSVMHEALHN~~ HYTQKSLSLSPG (SEQ ID NO: 5)	CDRs underlined; CH1=amino acids 118-215 (italicized); IgG1-P238K=amino acids 216-446; P238K underlined; no C-terminal lysine
	QVQLVQSGAEVKKPGSSSVKVSCKASGYAFT <u>S</u> <u>YWMH</u> WVRQAPGQGLEWMG <u>QINPTTGRSQYNE</u> <u>KFKT</u> RVTTITADKSTSTAYMELSSLRSED ~~TAV~~ YYCAR <u>WGLQPFAY</u> WGQGT ~~LVTVSS~~ ASTKGPS VFPLAPSSKSTSGGTAAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV TVPSSSLGTQTYICNVNHKPSNTKVDKRV KSCDKTHTCPPCPAPELLGGKSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTTPVLDSDGS FFLYSKLTVDKSRWQQGNVFS ~~CSVMHEALHN~~ HYTQKSLSLSPGK (SEQ ID NO: 6)	CDRs underlined; CH1=amino acids 118-215 (italicized); IgG1-P238K=amino acids 216-447; P238K underlined; C-terminal lysine present
Light chain variable region	DIQMTQSPSFLSASVGDRVTTITC <u>KASQDVST</u> <u>AVAWYQQKPGKAPKLLIY</u> <u>SASYRYT</u> GVP ~~S~~ RF	Vk-hz2 (SEQ ID NO: 10; CDRs underlined)

	SGSGSGTDFTLTISLQPEDFATYYC <u>QQHYS</u> <u>TPWTF</u> GGGKVEIK (SEQ ID NO: 10)	
VL-CDR1	KASQDVSTAVA (SEQ ID NO: 7)	Amino acids 24-34 of SEQ ID NO: 10
VL-CDR2	SASYRYT (SEQ ID NO: 8)	Amino acids 50-56 of SEQ ID NO: 10
VL-CDR3	QQHYSTPWT (SEQ ID NO: 9)	Amino acids 89-97 of SEQ ID NO: 10
LC_Y12XX- hz28	DIQMTQSPSFLSASVGDRVITITC <u>KASQDVST</u> <u>AVAWYQQKPGKAPKLLIY</u> <u>SASYRYT</u> GVPSRF SGSGSGTDFTLTISLQPEDFATYYC <u>QQHYS</u> <u>TPWTF</u> GGGKVEIKRTVAAPSVFIFPPSDEQ <i>LKSGTASVVCLLNNFYPREAKVQWKVDNALQ</i> <i>SGNSQESVTEQDSKSTYSLSSLTLSKADY</i> <i>EKKHVVYACEVTHQGLSSPVTKSFNRGEC</i> (SEQ ID NO: 11)	CDRs underlined; CL=amino acids 108- 214 (italicized)

[0040] An “antibody” (Ab) shall include, without limitation, an immunoglobulin, which binds specifically to an antigen and comprises at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, or an antigen-binding portion thereof. Each H chain comprises a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region comprises three constant domains, C_{H1}, C_{H2} and C_{H3}. Each light chain comprises a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region comprises one constant domain, C_L. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L comprises three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen.

[0041] An “antigen binding portion” of an Ab (also called an “antigen-binding fragment”) or antigen binding portion thereof refers to one or more sequences of an Ab (full length or fragment of the full length antibody) that retain the ability to bind specifically to the antigen bound by the whole Ab. Examples of an antigen-binding fragment include Fab, F(ab')₂, scFv (single-chain variable fragment), Fab', dsFv, sc(Fv)₂, and scFv-Fc.

[0042] A “humanized” antibody refers to an Ab in which some, most or all of the amino acids outside the CDR domains of a non-human Ab are replaced with corresponding

amino acids derived from human immunoglobulins. In one embodiment of a humanized form of an Ab, some, most, or all of the amino acids outside the CDR domains have been replaced with amino acids from human immunoglobulins, whereas some, most or all amino acids within one or more CDR regions are unchanged. Small additions, deletions, insertions, substitutions or modifications of amino acids are permissible as long as they do not abrogate the ability of the Ab to bind to a particular antigen. A “humanized” Ab retains an antigenic specificity similar to that of the original Ab.

[0043] A “chimeric antibody” refers to an Ab in which the variable regions are derived from one species and the constant regions are derived from another species, such as an Ab in which the variable regions are derived from a mouse Ab and the constant regions are derived from a human Ab.

[0044] As used herein, “specific binding” refers to the binding of an antigen by an antibody with a dissociation constant (K_d) of about 1 μ M or lower as measured, for example, by surface plasmon resonance (SPR). Suitable assay systems include the BIAcore™ (GE Healthcare Life Sciences, Marlborough, MA) surface plasmon resonance system and BIAcore™ kinetic evaluation software (e.g., version 2.1).

[0045] Binding of the present antibodies to CD40 antagonizes at least one CD40 activity. “CD40 activities” include, but are not limited to, T cell activation (e.g., induction of T cell proliferation or cytokine secretion), macrophage activation (e.g., the induction of reactive oxygen species and nitric oxide in the macrophage), and B cell activation (e.g., B cell proliferation, antibody isotype switching, or differentiation to plasma cells). CD40 activities can be mediated by interaction with other molecules. “CD40 activities” include the functional interaction between CD40 and the following molecules, which are identified by their Uniprot Accession Number in parentheses:

25	CALR	(P27797);
	ERP44	(Q9BS26);
	FBL	(P22087);
	POLR2H	(P52434);
	RFC5	(P40937);
30	SGK1	(O00141);
	SLC30A7	(Q8NEW0);

SLC39A7 (Q92504);
TRAF2 (Q5T1L5);
TRAF3 (Q13114);
TRAF6 (Q9Y4K3);
5 TXN (Q5T937);
UGGT1 (Q9NYU2); and
USP15 (Q9Y4E8).

[0046] For example, a CD40 “activity” includes an interaction with TRAF2. CD40/TRAF2 interaction activates NF- κ B and JNK. See Davies et al., Mol. Cell Biol. 25: 9806-19 (2005). This CD40 activity thus can be determined by CD40-dependent cellular NF- κ B and JNK activation, relative to a reference.

[0047] As used herein, the terms “activate,” “activates,” and “activated” refer to an increase in a given measurable CD40 activity by at least 10% relative to a reference, for example, at least 10%, 25%, 50%, 75%, or even 100%, or more. A CD40 activity is “antagonized” if the CD40 activity is reduced by at least 10%, and in an exemplary embodiment, at least about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 97%, or even 100% (i.e., no detectable activity), relative to the absence of the antagonist. For example, an antibody may antagonize some or all CD40 activity, while not activating CD40. For example, the antibody may not activate B cell proliferation. The antibody may not activate cytokine secretion by T cells, where the cytokine is at least one cytokine selected from the group consisting of IL-2, IL-6, IL-10, IL-13, TNF- α , and IFN- γ .

[0048] Variable domains may comprise one or more framework regions (FR) with the same amino acid sequence as a corresponding framework region encoded by a human germline antibody gene segment. Preferred framework sequences for use in the antibodies described herein are those that are structurally similar to the framework sequences used by antibodies described herein. The V_H CDR1, 2 and 3 sequences, and the V_L CDR1, 2 and 3 sequences, can be grafted onto framework regions that have the identical sequence as that found in the germline immunoglobulin gene from which the framework sequence derive, or the CDR sequences can be grafted onto framework regions that contain up to 20, preferably conservative, amino acid substitutions as compared to the germline sequences. For example, it has been found that in certain instances it is beneficial to mutate residues within the

framework regions to maintain or enhance the antigen binding ability of the antibody (see *e.g.*, U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al.*).

[0049] Exemplary framework regions are known in the art and described in U.S. Publication No. 2020-00157233. Exemplary heavy and light variable chains for a chimeric antibody are in Table 8 of the Examples in U.S. Publication No. 2020-00157233. The isolated antibody or antigen-binding portion thereof can be a humanized antibody. Exemplary humanized heavy and light variable chains are in Table 10 of the Examples in U.S. Publication No. 2020-00157233.

[0050] Exemplary CD40 antibodies of the present invention include an isolated antibody, or antigen binding portion thereof, that specifically binds to human CD40, wherein said antibody comprises a first polypeptide portion comprising a heavy chain variable region, and a second polypeptide portion comprising a light chain variable region, wherein:

said heavy chain variable region comprises a CDR1 comprising SYWMH (SEQ ID NO: 1), a CDR2 comprising QINPTTGRSQYNEKFKT (SEQ ID NO: 2), and a CDR3 comprising WGLQPFAY (SEQ ID NO: 3); and

said light chain variable region comprises a CDR1 comprising KASQDVSTAVA (SEQ ID NO: 7), a CDR2 comprising SASYRYT (SEQ ID NO: 8), and a CDR3 comprising QQHYSTPWT (SEQ ID NO: 9).

Fc Domain and Constant Region

[0051] The carboxyl-terminal "half" of a heavy chain defines a constant region (Fc) and which is primarily responsible for effector function. As used herein, the term "Fc domain" refers to the constant region antibody sequences comprising CH2 and CH3 constant domains as delimited according to Kabat et al., *Sequences of Immunological Interest*, 5th ed., U.S. Dept. Health & Human Services, Washington, D.C. (1991). The Fc region may be derived from a human IgG. In an embodiment, the Fc region may be derived from a human IgG1A heavy variable domain can be fused to an Fc domain. The carboxyl terminus of the variable domain may be linked or fused to the amino terminus of the Fc CH2 domain. Alternatively, the carboxyl terminus of the variable domain may be linked or fused to the amino terminus of a linker amino acid sequence, which itself is fused to the amino terminus of an Fc domain. Alternatively, the carboxyl terminus of the variable domain may be linked or fused to the amino terminus of a CH1 domain, which itself is fused to the Fc CH2 domain. Optionally, the protein may comprise the hinge region after the CH1 domain, in whole, or in

part. Optionally an amino acid linker sequence is present between the variable domain and the Fc domain. The carboxyl terminus of the light variable domain may be linked or fused to the amino terminus of a CL domain.

[0052] An exemplary sequence for a heavy chain CH1 is amino acids 118-215 of SEQ ID NO: 5 (ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV; SEQ ID NO: 23). An exemplary sequence for a light chain CL is amino acids 108-214 of SEQ ID NO: 11 (RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC; SEQ ID NO: 24).

[0053] The antibody can be a fusion antibody comprising a first variable domain that specifically binds human CD40, and a second domain comprising an Fc domain.

[0054] Exemplary Fc domains used in the fusion protein can include human IgG1 domains. While human IgG heavy chain genes encode a C-terminal lysine, the lysine is often absent from endogenous antibodies as a result of cleavage in blood circulation. Antibodies having IgG heavy chains including a C-terminal lysine, when expressed in mammalian cell cultures, may also have variable levels of C-terminal lysine present (Cai et al, 2011, *Biotechnol. Bioeng.* 108(2): 404-12). Accordingly, the C-terminal lysine of any IgG heavy chain Fc domain disclosed herein may be omitted.

[0055] The isolated antibody or antigen binding portion thereof described herein can comprise a human IgG1 Fc domain comprising a mutation at Kabat position 238 that reduces binding to Fc-gamma-receptors (FcγRs), wherein proline 238 (P238) is mutated to one of the residues selected from the group consisting of lysine (K), serine (S), alanine (A), arginine (R) and tryptophan (W), and wherein the antibody or antigen binding portion thereof has reduced FcγR binding. The isolated antibody or antigen binding portion thereof described herein can have P238 mutated to lysine in a human IgG1 Fc domain.

[0056] The isolated antibody or antigen binding portion thereof comprises an Fc domain, which comprises an amino acid sequence selected from: SEQ ID NOs: 13-20.

[0057] Exemplary sequences comprising the IgG1 Fc domains above include: SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 21, and SEQ ID NO: 22.

[0058] The isolated antibody or antigen binding portion thereof disclosed herein may be Y12XX-hz28-P238K having a) a heavy chain of SEQ ID NO: 5 or 6, and b) a light chain of SEQ ID NO: 11.

[0059] In a specific embodiment, the method of the present disclosure comprises administering BMS-986325. The amino acid sequences of the heavy chain and the light of BMS-986325 are depicted in Figure 1. Thus, in a specific embodiment, the method comprise administering an isolated antibody or antigen binding portion thereof having a heavy chain of SEQ ID NO: 5 and a light chain of SEQ ID NO: 11. BMS-986325 comprises the CDRs of humanized antibody Y12XX-hz28 (Vh-hz14; Vk-hz2) and a human IgG1 Fc domain comprising a lysine at Kabat position 238 (P238K).

[0060] BMS-986325 is an IgG1 isotype antibody containing a novel P238K mutation, that was engineered to abrogate Fc γ R binding to eliminate Fc-mediated signaling. As with other IgG molecules, BMS-986325 consists of two HCs and two LCs covalently bound by disulfide bonds. The resulting protein consists of a total of 1320 amino acid residues and has a molecular weight of 144,867 Da. The P238K mutation is located in the lower hinge region of the IgG1 constant domain as indicated in the primary sequence.

[0061] In nonclinical studies, the binding of BMS-986325 to CD40 from mouse, human, and cynomolgus monkey as well as to various Fc γ Rs has been evaluated by surface plasmon resonance (SPR). BMS-986325 has also been examined in assays for CD40 antagonism on both B cells and monocyte-derived dendritic cells (iDC). BMS-986325 has also been evaluated for antagonism on isolated B cells as well as WB B cells from cynomolgus monkeys. In addition, the lack of any agonist signal was confirmed in assays on both human and cynomolgus B cells as well as human immature DCs. A highly sensitive CD40-NF κ B reporter assay was used to further confirm lack of any agonist activity of BMS-986325. The summary of the in vitro and in vivo data is presented in Figures 2A-2C and Figure 3, respectively

[0062] The antibody or antigen binding portion thereof disclosed herein, wherein the antigen binding portion is selected from the group consisting of Fv, Fab, F(ab')₂, Fab', dsFv, scFv, sc(Fv)₂, diabodies, and scFv-Fc.

[0063] The antibody or antigen binding portion thereof disclosed herein can be an immunoconjugate, wherein the antibody or antigen-binding portion thereof is linked to a therapeutic agent.

[0064] The antibody or antigen-binding portion thereof disclosed herein can be a bispecific antibody, wherein the antibody or antigen-binding portion thereof is linked to a second functional moiety having a different binding specificity than said antibody or antigen binding portion thereof.

[0065] The antibody or antigen binding portion thereof disclosed herein can further comprise an additional moiety.

[0066] The variable regions of the present antibodies may optionally be linked to the Fc domain by an “amino acid linker” or “linker.” For example, the C-terminus of a variable heavy chain domain may be fused to the N-terminus of an amino acid linker, and an Fc domain may be fused to the C-terminus of the linker. Although amino acid linkers can be any length and consist of any combination of amino acids, the linker length may be relatively short (e.g., five or fewer amino acids) to reduce interactions between the linked domains. The amino acid composition of the linker also may be adjusted to reduce the number of amino acids with bulky side chains or amino acids likely to introduce secondary structure. Suitable amino acid linkers include, but are not limited to, those up to 3, 4, 5, 6, 7, 10, 15, 20, or 25 amino acids in length. Representative amino acid linker sequences include GGGGS (SEQ ID NO: 25), and a linker comprising 2, 3, 4, or 5 copies of GGGGS (SEQ ID NOs: 26 to 29, respectively). Table 3 lists suitable linker sequences for use in the present disclosure.

Table 3

Representative Linker Sequences

GGGGS	SEQ ID NO: 25
(GGGGS) ₂	SEQ ID NO: 26
(GGGGS) ₃	SEQ ID NO: 27
(GGGGS) ₄	SEQ ID NO: 28
(GGGGS) ₅	SEQ ID NO: 29
AST	SEQ ID NO: 30
TVAAPS	SEQ ID NO: 31
TVA	SEQ ID NO: 32
ASTSGPS	SEQ ID NO: 33

Antibody Preparation

[0067] The antibody can be produced and purified using ordinary skill in a suitable mammalian host cell line, such as CHO, 293, COS, NSO, and the like, followed by
5 purification using one or a combination of methods, including protein A affinity chromatography, ion exchange, reverse phase techniques, or the like.

[0068] As well known in the art, multiple codons can encode the same amino acid. Nucleic acids encoding a protein sequence thus include nucleic acids having codon degeneracy. The polypeptide sequences disclosed herein can be encoded by a variety of
10 nucleic acids. The genetic code is universal and well known. Nucleic acids encoding any polypeptide sequence disclosed herein can be readily conceived based on conventional knowledge in the art as well as optimized for production. While the possible number of nucleic acid sequence encoding a given polypeptide is large, given a standard table of the genetic code, and aided by a computer, the ordinarily skilled artisan can easily generate every
15 possible combination of nucleic acid sequences that encode a given polypeptide.

[0069] A representative nucleic acid sequence encoding the heavy chain variable domain of BMS-986325 including a constant region CH1 and Fc domain IgG1-P238K is:

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ATGAGGGCTT GGATCTTCTT TCTGCTCTGC CTGGCCGGGA GAGCGCTCGC  
ACAGGTGCAG CTGGTGCAGT CTGGTGCCGA GGTCAAAAAG CCAGGCTCCA  
20 GCGTGAAGGT GAGCTGCAAG GCCTCTGGCT ACGCTTTCAC CTCTTATTGG  
ATGCACTGGG TGAGACAGGC TCCTGGACAG GGCCTGGAGT GGATGGGCCA  
GATCAACCCA ACCACCGGCA GAAGCCAGTA CAATGAGAAG TTTAAGACCC  
GCGTGACCAT CACAGCCGAC AAGTCCACCA GCACAGCTTA TATGGAGCTG  
TCTTCCCTGA GGTCCGAGGA TACAGCCGTG TACTATTGCG CTCGGTGGGG  
25 CCTGCAGCCT TTCGCTTACT GGGGCCAGGG CACCCTGGTG ACAGTGAGCT  
CTGCTAGCAC CAAGGGCCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG  
AGCACCTCTG GGGGCACAGC GGCCCTGGGC TGCCTGGTCA AGGACTACTT  
CCCCGAACCG GTGACGGTGT CGTGGAATC AGGCGCCCTG ACCAGCGGCG  
TGCACACCTT CCCGGCCGTC CTACAGTCCT CAGGACTCTA CTCCTCAGC  
30 AGCGTGGTGA CCGTGCCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG  
CAACGTGAAT CACAAGCCCA GCAACACCAA GGTGGACAAG AGAGTTGAGC
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- CCAAATCTTG TGACAAAAC CACACATGCC CACCGTGCCC AGCACCTGAA
CTCCTGGGGG GAAAGTCAGT CTTCTCTTC CCCCCAAAAC CCAAGGACAC
CCTCATGATC TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA
GCCACGAAGA CCCTGAGGTC AAGTTCAACT GGTACGTGGA CGGCGTGGAG
5 GTGCATAATG CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA
CCGTGTGGTC AGCGTCCTCA CCGTCCTGCA CCAGGACTGG CTGAATGGCA
AGGAGTACAA GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG
AAAACCATCT CCAAAGCCAA AGGGCAGCCC CGAGAACCAC AGGTGTACAC
CCTGCCCCCA TCCCGGGATG AGCTGACCAA GAACCAGGTC AGCCTGACCT
10 GCCTGGTCAA AGGCTTCTAT CCCAGCGACA TCGCCGTGGA GTGGGAGAGC
AATGGGCAGC CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC
CGACGGCTCC TTCTTCTCT ACAGCAAGCT CACCGTGGAC AAGAGCAGGT
GGCAGCAGGG GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC
AACCACTACA CGCAGAAGAG CCTCTCCCTG TCTCCGGGTT GA (SEQ ID NO: 34).
- 15 In this sequence, nucleotides 1-51 encode a signal peptide (optional), nucleotides 52-402 encode the heavy chain variable region in which nucleotides 141-155 encode CDR1, nucleotides 198-249 encode CDR2, and nucleotides 346-369 encode CDR3 of the Y12XX variable domain of the heavy chain. Nucleotides 403-696 encode a CH1 domain, and nucleotides 697-1399 encode IgG1-P238K. Nucleotides 1400-1402 are a stop codon.
- 20 **[0070]** A representative nucleic acid sequence encoding the light chain variable domain of BMS-986325 including a constant region CL is:
- ATGAGGGCTT GGATCTTCTT TCTGCTCTGC CTGGCCGGGC GCGCCTTGGC
CGACATCCAG ATGACCCAGT CCCCCTCCTT CCTGTCTGCC TCCGTGGGCG
ACAGAGTGAC CATCACCTGT AAGGCTTCCC AGGATGTGAG CACAGCCGTG
25 GCTTGGTACC AGCAGAAGCC AGGCAAGGCC CCCAAGCTGC TGATCTATTC
CGCCTCTTAC AGGTATACCG GCGTGCCCTC TCGGTTCTCC GGCAGCGGCT
CTGGCACAGA CTTTACCCTG ACAATCTCCA GCCTGCAGCC TGAGGATTTC
GCCACCTACT ATTGCCAGCA GCACTACTCC ACCCCATGGA CATTTGGCGG
CGGCACCAAG GTGGAGATCA AGCGTACGGT GGCTGCACCA TCTGTCTTCA
30 TCTTCCCGCC ATCTGATGAG CAGTTGAAAT CTGGAAGTGC CTCTGTTGTG
TGCCTGCTGA ATAATTCTA TCCCAGAGAG GCCAAAGTAC AGTGGAAGGT

GGATAACGCC CTCCAATCGG GTAAC TCCCA GGAGAGTGTC ACAGAGCAGG
 ACAGCAAGGA CAGCACCTAC AGCCTCAGCA GCACCCTGAC GCTGAGCAAA
 GCAGACTACG AGAAACACAA AGTCTACGCC TCGGAAGTCA CCCATCAGGG
 CCTGAGCTCG CCCGTCACAA AGAGCTTCAA CAGGGGAGAG TGTTAG

- 5 (SEQ ID NO: 35). In this sequence, nucleotides 1-51 encode a signal peptide (optional), nucleotides 52-372 encode the light chain variable region in which nucleotides 121-153 encode CDR1, nucleotides 199-219 encode CDR2, and nucleotides 316-342 encode CDR3. Nucleotides 373-693 encode a CL. Nucleotides 694-696 are a stop codon

- [0071] The coding sequence for the heavy and/or light chain optionally may encode a signal peptide, such as MRAWIFLLCLAGRALA (SEQ ID NO: 36), at the 5' end of the coding sequence. As described above, an exemplary nucleic acid coding sequence for this signal peptide is

ATGAGGGCTT GGATCTTCTT TCTGCTCTGC CTGGCCGGGA GAGCGCTCGC A (SEQ ID NO: 37).

- 15 [0072] Accordingly, a nucleic acid encoding an antibody disclosed herein is also contemplated. Such a nucleic acid may be inserted into a vector, such as a suitable expression vector, e.g., pHEN-1, for expression in an isolated cell (Hoogenboom et al. (1991) *Nucleic Acids Res.* 19: 4133-4137). Further provided is an isolated host cell comprising the vector and/or the nucleic acid.

- 20 [0073] The antibody of the disclosure can be produced and purified using only ordinary skill in any suitable mammalian host cell line, such as CHO (Chinese hamster ovary cells), 293 (human embryonic kidney 293 cells), COS cells, NSO cells, and the like, followed by purification using one or a combination of methods, including protein A affinity chromatography, ion exchange, reverse phase techniques, or the like.

25 **Pharmaceutical Compositions and Methods of Treatment**

- [0074] A pharmaceutical composition comprises a therapeutically-effective amount of one or more antibodies and optionally a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers include, for example, water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. Pharmaceutically acceptable carriers can further comprise minor amounts of auxiliary substances, such as wetting or emulsifying agents, preservatives, or buffers that enhance the shelf-life or effectiveness of the fusion protein. The compositions can be
- 30

formulated to provide quick, sustained, or delayed release of the active ingredient(s) after administration. Suitable pharmaceutical compositions and processes for preparing them are known in the art. *See, e.g.,* Remington, THE SCIENCE AND PRACTICE OF PHARMACY, A. Gennaro, et al., eds., 21st ed., Mack Publishing Co. (2005).

- 5 **[0075]** In an embodiment, a pharmaceutical composition comprises an antibody or antigen-binding portion thereof described herein in a formulation comprising histidine, sucrose, pentetic acid and polysorbate. In an embodiment, the formulation comprising 150 mg/ml antibody, 20 mM histidine, 250 mM sucrose, 50 micromolar pentetic acid and 0.05% (w/v) polysorbate 80, pH 6.0. The formulation may be buffered with a sodium acetate buffer
10 or a sodium phosphate buffer. In an embodiment, the pharmaceutical composition comprises or consists of 150 mg/ml BMS-986325, 20 mM histidine, 250 mM sucrose, 50 micromolar pentetic acid and 0.05% (w/v) polysorbate 80, pH 6.0.

- [0076]** The pharmaceutical composition may be administered alone or in combination therapy, (i.e., simultaneously or sequentially) with an immunosuppressive/immuno-
15 modulatory and/or anti-inflammatory agent. An exemplary type of agent is a cytotoxic T lymphocyte-associated protein 4 (CTLA4) mutant molecule. An exemplary CTLA4 mutant molecule is L104EA29Y-Ig (belatacept) which is a modified CTLA4-Ig. Different immune diseases can require use of specific auxiliary compounds useful for treating immune diseases, which can be determined on a patient-to-patient basis. For example, the pharmaceutical
20 composition may be administered in combination with one or more suitable adjuvants, e.g., cytokines (IL-10 and IL-13, for example) or other immune stimulators, e.g., chemokines, tumor-associated antigens, and peptides. Suitable adjuvants are known in the art.

- [0077]** A method of treating an autoimmune disease in a patient in need of such treatment may comprise administering to the patient a therapeutically effective amount of the
25 antibody, or antigen binding portion thereof, as described herein. Also provided herein is the use of an antibody, or antigen-binding portion thereof or treating an autoimmune disease in a patient in need of such treatment and/or for treating or preventing an autoimmune disease in a patient in need of such treatment, that may comprise administering to the patient a therapeutically effective amount of the antibody, or antigen binding portion thereof.
30 Antagonizing CD40-mediated T cell activation could inhibit undesired T cell responses occurring during autoimmunity. Inhibiting CD40-mediated T cell activation could moderate the progression and/or severity of these diseases.

[0078] The use of an antibody, or antigen-binding portion thereof, of the disclosure, in the preparation of a medicament for treating or preventing an autoimmune disease in a patient in a patient in need of such treatment, is also provided. The medicament can, for example, be administered in combination with an immunosuppressive/immunomodulatory and/or anti-inflammatory agent.

[0079] As used herein, a “patient” means an animal, e.g., mammal, including a human. In the method disclosed herein, the patient may be diagnosed with an autoimmune disease. “Treatment” or “treat” or “treating” refers to the process involving alleviating the progression or severity of a symptom, disorder, condition, or disease. An “immune disease” refers to any disease associated with the development of an immune reaction in an individual, including a cellular and/or a humoral immune reaction. Examples of immune diseases include, but are not limited to, inflammation, allergy, autoimmune disease, or graft-related disease. In the present application, the method is directed to treatment of an autoimmune disease. An “autoimmune disease” refers to any disease associated with the development of an autoimmune reaction in an individual, including a cellular and/or a humoral immune reaction. An example of an autoimmune disease is Sjögren’s syndrome. Treatment of primary Sjögren’s syndrome (pSS) as well as secondary Sjögren’s syndrome is encompassed. Other autoimmune diseases include inflammatory bowel disease (IBD) including, but not limited to ulcerative colitis and Crohn’s disease, systemic lupus erythematosus (SLE), lupus nephritis, multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes, psoriasis, scleroderma, and atherosclerosis.

[0080] The pharmaceutical composition may be administered alone or as a combination therapy, (i.e., simultaneously or sequentially) with an immunosuppressive/immunomodulatory and/or anti-inflammatory agent. Different autoimmune diseases can require use of specific auxiliary compounds useful for treating autoimmune diseases, which can be determined on a patient-to-patient basis. For example, the pharmaceutical composition may be administered in combination with one or more suitable adjuvants, e.g., cytokines (IL-10 and IL-13, for example) or other immune stimulators, e.g., chemokines, tumor-associated antigens, and peptides. Suitable adjuvants are known in the art.

[0081] Any suitable method or route can be used to administer the antibody, or antigen-binding portion thereof, or the pharmaceutical composition. Routes of administration

include, for example, intravenous (IV), intraperitoneal, subcutaneous (SC), or intramuscular administration. In an embodiment, the antibody, or antigen binding portion thereof, or the pharmaceutical composition is administered subcutaneously or intravenously.

[0082] The frequency of administration depends on numerous factors including, for example, the type and severity of the autoimmune disease being treated, the use of combination therapy, the route of administration of the antibody, or antigen binding portion thereof, or pharmaceutical composition, and the weight of the patient. The antibody polypeptide can be administered daily, weekly, biweekly (once every 2 weeks), every 2-3 weeks, every 3-4 weeks, or monthly. The duration of treatment similarly depends on numerous factors. Treatment can comprise a single dose, or one or more doses. Treatment can be administered regularly over weeks, months, or years, or sporadically on an as-needed basis.

[0083] Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced, or increased as needed in response to the treatment. Formulating pharmaceutical compositions for use in intravenous (IV), intraperitoneal, subcutaneous (SC), or intramuscular administration in dosage unit form is useful for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0084] A "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that, when used alone or in combination with another therapeutic agent, promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a prevention of impairment or disability due to the disease affliction. A therapeutically effective dose of administered antibody depends on numerous factors, including, for example, the type and severity of the autoimmune disease being treated, the use of combination therapy, the route of administration of the antibody, or antigen binding portion thereof, or pharmaceutical composition, and the weight of the patient. A non-limiting range for a therapeutically effective amount of the anti-CD40 monoclonal antibody is 0.1-20

milligram/kilogram (mg/kg), and in an aspect, 1-10 mg/kg, relative to the body weight of the patient.

[0085] A non-limiting range for a therapeutically effective amount of the anti-CD40 monoclonal antibody wherein the heavy chain variable region comprises (i) a CDR1 comprising SYWMH (SEQ ID NO: 1), a CDR2 comprising QINPTTGRSQYNEKFKT (SEQ ID NO: 2), and a CDR3 comprising WGLQPFAY (SEQ ID NO: 3), and the light chain variable region comprises a CDR1 comprising KASQDVSTAVA (SEQ ID NO: 7), a CDR2 comprising SASRYT (SEQ ID NO: 8), and a CDR3 comprising QQHYSTPWT (SEQ ID NO: 9); and (ii) a human IgG1 Fc domain comprising a mutation at Kabat position 238 that reduces binding to Fc-gamma-receptors (Fc γ Rs), is from 0.3 milligram (mg) to 1000 mg for intravenous (IV) administration and from 100 mg to 1000 milligram for subcutaneous (SC) administration.

[0086] In an embodiment, the administration may be intravenous (IV) and the dose is from 0.3 to 1000 milligrams (mg) of the antibody polypeptide. The dose may be selected from 0.3, 1, 3, 10, 30, 100, 150, 300, 600, or 1000 mg of the antibody polypeptide. The method may comprise more than one iteration of the administering step. The method may comprise intravenous (IV) administration, where the dose is from 100 to 600 mg of the antibody polypeptide, and the method comprises at least four iterations of the administering step. In an embodiment, dosing is once a week (QW) for at least four iterations of the administering step. For instance, a dose of 100 mg, 150 mg, 200 mg, or 300 mg is administered on week for at least four iterations. In another embodiment, dosing is once every two weeks (q2wk) with at least two iterations of the administering step. For instance, a dose of 200 mg, 300 mg, 400 mg, or 600 mg is administered every two weeks to the patient for at least two iterations. In an embodiment, the initial dose is higher than the subsequent doses. For instance, the initial dose is 300 mg and subsequent doses are 100 mg.

[0087] Exemplary intravenous (IV) doses include, but are not limited to, 0.1 mg, 0.5 mg, 0.8, 1 mg, 3, mg, 10mg, 30mg, 50 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 320 mg, 340 mg, 360 mg, 380 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg, 620 mg, 640 mg, 660 mg, 680 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, and 1000 mg of antibody polypeptide. Exemplary IV doses include, but are not limited to, 80 mg, 90

mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, and 1000 mg of antibody polypeptide. In an embodiment, the antibody is BMS 986325. In an embodiment, the IV dose is 75 to 100 mg, or 90 mg. In an embodiment, the IV dose is 75 to 100 mg, or 90 mg administered weekly (qwk). In an embodiment, an IV dose is 75 to 100 mg, or 90 mg is administered weekly (qwk) for at least 4 weeks. In an embodiment, the IV dose is 75 to 100 mg, or 90 mg of BMS 986325. In an embodiment, the IV dose is 75 to 100 mg, or 90 mg of BMS 986325 administered weekly (qwk). In an embodiment, an IV dose is 75 to 100 mg, or 90 mg of BMS 986325 is administered weekly (qwk) for at least 4 weeks. In an embodiment, an IV dose is 150 to 200 mg, or 180 mg of BMS 986325 is administered every other week for at least 4 weeks.

[0088] In an embodiment, the administration is subcutaneous (SC) and the dose is from 100 to 1000 mg of the antibody polypeptide. The dose may be selected from 100 mg, 300 mg, 600 mg, or 1000 mg of the antibody polypeptide. The method may comprise more than one iteration of the administering step. The method may comprise sub-cutaneous administration, where the dose is selected from 100 mg to 600 mg, such as 100 mg, 300 mg or 600 mg of the antibody polypeptide. In an embodiment, the initial dose is higher than the subsequent doses.

[0089] Exemplary ranges for SC doses include, but are not limited to, 50 mg to 1000 mg, 50 mg to 750 mg, 75 mg to 700 mg, 100 mg to 1000 mg, 100mg to 600 mg, 150 mg to 1000 mg, 150mg to 600 mg, 300 mg to 600 mg, 100 mg to 150 mg to 300 mg SC, and 150 mg to 300 mg to 600 mg SC of the antibody. SC doses include, but are not limited to, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, and 1000 mg of antibody polypeptide. Exemplary SC doses include, but are not limited to, 100 mg, 150 mg, 240 mg, 250 mg, 300 mg, and 600 mg of antibody polypeptide. In an embodiment, the antibody is BMS 986325. In an embodiment, the SC dose is 200 to 300 mg or 240 mg. In an embodiment, the SC dose is 200 to 300 mg or 240 mg administered one every two weeks (q2wk). In an embodiment, an SC dose of 100 mg is administered weekly for at least 4 weeks, or an SC dose of 300 mg is administered weekly for at least 4 weeks, or an SC dose of 600 mg is administered weekly for at least 4 weeks. In an embodiment, the SC dose of BMS 986325 is 200 to 300 mg or 240 mg. In an embodiment, the SC dose is 200 to 300 mg

or 240 mg of BMS 986325 administered one every two weeks (q2wk). In another embodiment, an SC dose of 100 mg of BMS 986325 is administered weekly for at least 4 weeks, or an SC dose of 300 mg of BMS 986325 is administered weekly for at least 4 weeks, or an SC dose of 600 mg of BMS 986325 is administered weekly for at least 4 weeks, or an SC dose of 600 mg of BMS 986325 is administered once every other week for at least 4 weeks.

[0090] The dose of antibody polypeptide(s) can be further guided by the amount of antibody polypeptide(s) required for CD40 antagonism in *in vitro* and/or *in vivo* models of disease states. Representative models are described in the examples.

10 Kits

[0091] A kit useful for treating an autoimmune disease such as Sjögren's syndrome in a human patient is provided. The kit can comprise (a) a dose of an antibody, or antigen binding portion thereof of the present disclosure, and (b) instructional material for using the antibody, or antigen binding portion thereof, in the method of treating an immune disease, or for using the antibody, or antigen binding portion thereof, in the method of treating or preventing an autoimmune or inflammatory disease, in a patient. For example, the antibody, or antigen-binding portion thereof can be BMS 986325. In an embodiment, the dose ranges from 1 milligram (mg) to 1000 mg. In an embodiment, the dose of antibody BMS-986325 is a formulation comprising 20 mM histidine, 250 mM sucrose, 50 micromolar pentetic acid and 0.05% (w/v) polysorbate 80, pH 6.0. The formulation may comprise a sodium acetate buffer or a sodium phosphate buffer.

[0092] "Instructional material," as that term is used herein, includes a publication, a recording, a diagram, or any other medium of expression, which can be used to communicate the usefulness of the composition and/or compound of the invention in a kit. The instructional material of the kit may, for example, be affixed to a container or contained within the confines of the kit or the container, which contains the compound and/or composition of the invention or be shipped together with a container, which contains the compound and/or composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the recipient uses the instructional material and the compound cooperatively. Delivery of the instructional material may be, for example, by physical delivery of the publication or other medium of expression communicating the usefulness of

the kit, or may alternatively be achieved by electronic transmission, for example by means of a computer, such as by electronic mail, or download from a website.

EXAMPLES

Example 1: Kinetics of Binding to Human and Cynomolgus CD40

5 [0093] The kinetics and affinity of BMS-986325 binding to human CD40 and cynomolgus CD40 were characterized by surface plasmon resonance (SPR), by capturing BMS-986325 on an immobilized protein A sensor chip surface and testing the binding of multiple concentrations of monomeric human CD40 or cynomolgus CD40 analyte. BMS-986325 was found to bind to human CD40 with a dissociation constant (Kd) of 5.3 nM, and
10 to cynomolgus CD40 with a Kd of 6.7 nM. See Table 4. BMS-986325 was also tested for binding to murine CD40 and rat CD40 in a single-cycle kinetic SPR assay, where BMS-986325 demonstrated strong binding to the human CD40 and cynomolgus CD40 surfaces; no detectable binding to either murine CD40 or rat CD40 was observed (data not shown).

Table 4 Determination of CD40 Target-binding Properties of BMS-986325 by Surface Plasmon Resonance

Target	ka (1/Ms)	kd (1/s)	Kd (nM)
Human CD40	2.3×10^5	1.2×10^{-3}	5.3
Cynomolgus CD40	2.4×10^5	1.6×10^{-3}	6.7

15

Example 2: Binding to FcγRs

[0094] BMS-986325 comprises a novel IgG1-P238K isotype, which was engineered to reduce FcγR binding and FcγR2; or cynomolgus FcγRs (cyCD32a, cyCD32b, cyCD16. See Table 5. Further, binding of BMS-986325 to the high-affinity human CD64 or
20 cynomolgus CD64 FcγRs was more than 100-fold weaker than binding of wild-type human IgG1 control. See Table 5.

Table 5: FcγR Binding Properties of BMS-986325

FcγR	IgG1 Kd (nM)	BMS-986325 Kd (nM)
hCD64	< 0.1	17
hCD32a-H131	446	NB
hCD32a-R131	665	NB
hCD32b	3,090	NB
hCD16a-V158	119	NB
hCD16a-F158	4,430	NB
cyCD64	< 0.1	13
cyCD32a	1,520	NB
cyCD32b	877	NB
cyCD16	164	NB

Abbreviations: NB, no detectable binding.

Example 3: Summary of Non-Clinical Pharmacokinetics Evaluation of BMS-986325

[0095] The pharmacokinetics (PK) of BMS-986325 (Y12XX-hz28-P238K) were evaluated in mice and cynomolgus monkeys. Since BMS-986325 does not cross react to murine CD40 receptors, the PK evaluated in mice is intrinsic or non-specific PK. BMS-986325 cross reacts with monkey CD40 receptors, therefore the total PK (specific and non-specific PK) was evaluated in monkeys. After intravenous (IV) administration of BMS-986325 (single 1- and 10-mg/kg doses) to mice, BMS-986325 exhibited low total serum clearance “CLT” of 0.5 to 1.02 mL/d/kg, limited volume of distribution at steady state “Vss” of 0.12 to 0.19 L/kg, and long apparent elimination half-life “T-HALF” of 118 to 183 hours (~ 5 to 8 days).

[0096] In monkeys, a single subcutaneous (SC) dose (10 mg/kg) of BMS-986325 was administered. The dose administered is a dose at which specific clearance (target-mediated drug disposition “TMDD”) is not saturated. After the single SC dose, BMS-986325 was well absorbed, with an absolute bioavailability of 70.4% (relative to exposures at the same IV dose). After IV administration of BMS-986325 (10 mg/kg single dose) to monkeys, BMS-986325 exhibited a CLT of 0.41 mL/d/kg, a limited Vss of 0.05 L/kg, and a T-HALF of 100 hours (~ 4 days). The time to maximum plasma concentration “Tmax” following a single SC dose of BMS-986325 (doses of 1, 10, and 100 mg/kg administered) to monkeys was 24 to 54

hours. There were more-than-dose-proportional increases in exposure (maximum concentration “C_{max}” and area under the concentration vs time curve extrapolated from time zero to infinity “AUC[INF]”) and an increase in T-HALF with dose (~ 31, ~ 119, and ~197 hours at 1, 10, and 100 mg/kg dose, respectively). These data suggest non-linear PK and a saturable clearance mechanism; this likely results from target (CD40)-mediated clearance, reflecting TMDD. In this single-dose PK study, anti-drug antibody (ADA) formation was detected in ~ 50% of monkeys, but had no apparent impact on the overall PK parameters.

[0097] Pharmacokinetic/pharmacodynamic modeling TMDD model with quasi steady-state assumption (TMDD-Qss) was used to describe the nonlinear PK observed in monkeys, establish a relationship between serum drug exposure and CD40 receptor occupancy (RO) and subsequent human dose projection.

Example 4: Pharmacokinetic/Pharmacodynamic Modeling of Data from Single-dose Study in Monkeys (Study DN18016) and Projection of Human Pharmacokinetics and Efficacious Dose

15 [0098] PK/PD modeling was used to describe the nonlinear PK observed in monkeys and establish a relationship between serum drug exposure and CD40 RO. BMS-986325 exhibited nonlinear PK (greater-than-dose-proportional increases in exposure and an increase in T-HALF with dose), which are characteristics of a saturable clearance mechanism resulting from TMDD. To describe the nonlinear PK of BMS-986325 observed in monkeys, a target-mediated drug disposition model with quasi steady-state assumption (TMDD-Qss model) was used to account for nonspecific (linear), and specific or CD40 target-mediated (nonlinear) clearance processes. The drug concentrations and RO data from monkeys were simultaneously fitted to the PK/PD model. The model-fitted curves described both the PK and RO profiles, demonstrating that the CD40 receptor-mediated binding and disposition are responsible for the nonlinear PK of BMS-986325.

[0099] The human PK of BMS-986325 was predicted using the same PK/PD model used to describe the PK and RO of BMS-986325 in monkeys. To predict human PK parameters, the CLT, V_{ss}, and T-HALF of BMS-986325 in monkeys in the absence of TMDD were calculated. For the nonspecific elimination or linear clearance component, the model-derived nonspecific clearance in monkeys (0.34 mL/h/kg) was allometrically scaled to that in humans (0.23 mL/h/kg) using an exponent of 0.85. The human V_{ss} (0.08 L/kg) was also allometrically predicted from monkey data (0.08 L/kg) using an exponent of 1. The T-HALF

in human was calculated to be 13 days (10 days in monkeys). The TMDD in humans was assumed to be same as in monkeys. The bioavailability of BMS-986325 after SC administration in humans was assumed to be the same as in monkeys.

- [00100]** Assuming the same PK/PD relationship exists between monkey and human, and based on estimated human PK parameters and steady-state trough plasma concentrations of 0.03 to 0.4 μM , the efficacious doses of BMS-986325 to achieve RO of 90%, 95%, and 99% in humans were projected (Table 6). Complete KLH-mediated TDAR suppression was achieved at RO of > 95% with BMS-986325 in monkeys and BMS-986090 in humans.

Table 6: Projected Human Efficacious Doses of BMS-986325 in Humans

Receptor Occupancy	Projected Efficacious SC Dose of BMS-986325 in Humans ^a	
	Every-week	Every-2-weeks
90%	66 mg	275 mg
95%	90 mg	240 mg
99%	180 mg	775 mg

^a In a 70-kg normal healthy human subject.

10 **Example 5: Clinical Study of BMS-986325 in human subjects**

- [00101]** The clinical trial protocol entitled “Clinical Protocol IM039-004 A Double-Blind, Placebo-Controlled, Randomized, Single and Multiple Dose Study on the Safety, Pharmacokinetics and Pharmacodynamics of Subcutaneous and Intravenous BMS-986325 Administration in Healthy Participants and Participants with Primary Sjögren’s Syndrome” describes in detail a clinical trial protocol and is appended to the present application. Excerpts of the protocol are provided below.

- [00102]** To date, BMS-986325 has not been administered to humans. The proposed First-in-Human (FIH) study for BMS-986325 will include single- and multiple-ascending dose (SAD and MAD), placebo-controlled cohorts of healthy participants (Parts A and B) and cohorts of participants with primary Sjögren’s syndrome (Part C), via IV and/or SC administration routes under a combined protocol. The objective of this initial study is to evaluate the safety, tolerability, PK, PD (e.g., biomarker response), immunogenicity, bioavailability and disease effects of BMS-986325, using doses and duration of dosing guided by the initial toxicology program, and by data emerging from the study itself.

[00103] The proposed SAD starting dose and top dose is 0.3 mg and 1000 mg, respectively, supported by minimum anticipated biological effect level (MABEL), pharmacologically active dose (PAD), and NOAEL approaches. Dose escalation decisions will be based on evaluation of available results from the ongoing cohorts including safety and tolerability, clinical laboratory assessments, and possibly available PK, PD, and target engagement data. If BMS-986325 exhibits a profile supportive of further development, studies in participants with select immune-mediated diseases would be planned.

Human Dosing Range and Safety Margins

[00104] The Phase 1 FIH study of BMS-986325 (SAD and MAD) is proposed to be evaluated in healthy participants (Parts A and B) and in participants with Sjögren's syndrome (Phase 1b, Part C). The proposed dose ranges to be evaluated in the SAD portion of the study (Part A) are 0.3-1000 mg (9 dose levels) IV (*see* Figure 4). In the MAD portion of the study (Part B), weekly SC injections of 100, 300, and 600 mg administered for 4 weeks will be evaluated. Dosing in Part C will not exceed safe exposure in SAD/MAD, with duration of dosing limited to 4 weeks and frequency of dosing not more than once weekly.

Selection of BMS-986325 Starting Dose for the FIH Study

[00105] The primary objective of the FIH clinical study (IM039-004) is to characterize the safety and tolerability of SAD and MAD doses of BMS-986325 in healthy participants (Parts A and B), and multiple doses in participants with Sjögren's syndrome (Part C).

[00106] To select the starting dose, both MABEL ("minimum anticipated biological effect level") and NOAEL ("no observed adverse effect dose level") approaches were employed. The MABEL dose was defined as a dose at which the maximum CD40 RO in human WB is approximately 40%. The starting dose of 0.3 mg IV is projected to provide CD40 RO of 39.5% at C_{max}. At this RO level, the pharmacological activity is anticipated to be minimal based on results from ex vivo CD40L-driven B-cell activation (CD86) assay and KLH-induced TDAR in the single-dose PK/PD study in cynomolgus monkeys. Additionally, previous experience in the clinic with anti-CD40 dAb BMS-986090 demonstrated a maximum RO achievement of 8% and 42% at 3 and 10 mg SC doses, respectively. As neither RO coverages resulted in an inhibition of TDAR (T-cell-dependent antibody responses), it is highly unlikely the proposed starting dose of 0.3 mg IV, which is projected to provide an RO of 39.5% (at C_{max}), would trigger any TDAR suppression.

[00107] The 1-month toxicity study in monkeys at weekly doses of up to 100 mg/kg (IV) showed that BMS-986325 was well tolerated at all doses with effects consistent with its pharmacology. See Figure 5. Based on the results of that study, the NOAEL was considered to be 100 mg/kg IV. The predicted C_{max} and AUC(INF) (area under the concentration versus time curve extrapolated from time zero to infinity after IV administration of the starting dose (0.3 mg) are 0.09 µg/mL and 0.57 µg•h/mL, respectively, based on predicted human PK (Figure 5). The starting dose of 0.3 mg BMS-986325 IV is projected to provide an exposure safety margin that is 1,192,982-fold below the assessed NOAEL in terms of AUC and 26,111-fold below for C_{max} (Figure 5).

10 Selection of Top Dose and Dose Range

[00108] The proposed top dose in SAD is 1000 mg administered as IV infusion. The dose needs be tested in case significant TMDD is observed in patients with immune-mediated disease, which may require loading dose in future studies, as shown in Phase 2a study of iscalimab in patients with primary Sjögren's syndrome. The dose of 1000 mg BMS-986325 IV is projected to provide a CD40 RO of 99% (at C_{max}) and an exposure that is 6- and 14-fold by C_{max} and AUC, respectively, below the NOAEL exposure (100 mg/kg/week) assessed in the 1-month monkey toxicology study. See Figure 5.

[00109] The efficacious human dose is predicted to be 90 mg qwk or 240 mg q2wk for maintaining a trough RO of > 95 %, assuming the same PK profile in participants with Sjögren's syndrome as in healthy participants. The SAD dose escalation scheme and the corresponding predicted human PK, RO and safety multiples based on NOAEL and MABEL approach are summarized in Figure 4.

[00110] Overall, the proposed doses for this study will span the anticipated efficacious dose-range projected for meaningful PD effects and are considered to be within an appropriate safety margin indicated by the nonclinical toxicology results. Dose escalation decisions for the SAD study will depend on a thorough evaluation of the safety, tolerability (including reported AEs, findings from physical examinations, clinical laboratory results, vital signs, ECGs and safety PD biomarkers), and any available PK and RO data for each dose cohort.

[00111] Although the present embodiments have been described in detail with reference to examples above, it is understood that various modifications can be made without departing from the spirit of these embodiments, and would readily be known to the skilled artisan.

[00112] These and other aspects disclosed herein, including the exemplary specific treatment methods, medicaments, and uses listed herein, will be apparent from the teachings contained herein.

WHAT IS CLAIMED IS:

1. A method of treating an autoimmune disease such as Sjögren's syndrome in a human patient, the method comprising administering to the patient in need thereof at least one dose of an isolated antibody, or antigen-binding portion thereof, that specifically binds to human CD40, wherein the antibody or antigen binding portion thereof comprises a first polypeptide portion comprising a heavy chain variable region, and a second polypeptide portion comprising a light chain variable region, wherein:
- the heavy chain variable region comprises (i) a CDR1 comprising SYWMH (SEQ ID NO: 1), a CDR2 comprising QINPTTGRSQYNEKFKT (SEQ ID NO: 2), and a CDR3 comprising WGLQPFAY (SEQ ID NO: 3); and
- the light chain variable region comprises a CDR1 comprising KASQDVSTAVA (SEQ ID NO: 7), a CDR2 comprising SASYRYT (SEQ ID NO: 8), and a CDR3 comprising QQHYSTPWT (SEQ ID NO: 9),
- wherein the dose is selected from 0.3 milligram (mg) to 1000 mg of the antibody, or antigen binding portion thereof.
2. The method of claim 1, wherein the autoimmune disease is Sjögren's syndrome.
3. The method of claim 1 or 2, wherein the isolated antibody or antigen-binding portion thereof comprises a human IgG1 Fc domain comprising a mutation at Kabat position 238 that reduces binding to Fc-gamma-receptors (FcγRs), wherein proline 238 (P238) is mutated to one of the residues selected from the group consisting of lysine, serine, alanine, arginine, and tryptophan.
4. The method of any one of the preceding claims, wherein the administration is sub-cutaneous and the dose is from 100 mg to 1000 mg of the antibody or antigen-binding portion thereof.

5. The method of any one of the preceding claims, wherein the administration is sub-cutaneous and the dose is 100 mg, 200 mg, 300 mg, 600 mg, or 1000 mg of the antibody or antigen-binding portion thereof.

5 6. The method of any one of the preceding claims, wherein the administration is sub-cutaneous, the dose is from 100 mg to 1000 mg of the antibody or the antigen-binding portion thereof, and the method comprises at least four iterations of the administering step.

10 7. The method of any one of the preceding claims, wherein the administration is sub-cutaneous, the dose is from 100 to 600 mg of the antibody administered weekly, and the method comprises at least four iterations of the administering step.

15 8. The method of any one of claims 1-3, wherein the administration is intravenous and the dose is from 0.3 mg to 1000 mg of the antibody or antigen-binding fragment thereof.

 9. The method of claim 8, wherein the administration is intravenous, and the dose is from 100 mg, 150 mg, 300 mg, or 600 mg of the antibody or antigen-binding fragment thereof.

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 10. The method of claim 8 or 9, wherein the administration is intravenous and the dose is selected from 100 mg, 300 mg, or 600 mg of the antibody, and the method comprises at least four iterations of the administering step.

25 11. The method of any one of claims 8-10, wherein the administration is intravenous and the dose is selected from 100 mg, 300 mg, or 600 mg of the antibody or the antigen-binding fragment thereof administered weekly, and the method comprises at least four iterations of the administering step

12. The method of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is administered in combination with an immunosuppressive/immunomodulatory and/or anti-inflammatory agent.

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13. The method of claim 12, wherein the antibody or antigen-binding fragment thereof and the immunosuppressive/immunomodulatory and/or anti-inflammatory agent are administered sequentially.

10 14. The method of claim 12, wherein the antibody or antigen-binding fragment thereof and the immunosuppressive/immunomodulatory and/or anti-inflammatory agent are administered simultaneously.

15 15. The method of claim 12, wherein the antibody or antigen-binding fragment thereof and the immunosuppressive/immunomodulatory and/or anti-inflammatory agent are formulated in a single composition.

16. The method of any one of claims 1-15, wherein the antibody, or antigen binding portion thereof, comprises a first polypeptide portion comprising a heavy chain variable region, and a second polypeptide portion comprising a light chain variable region, wherein:

the heavy chain variable region comprises the amino acid sequence of
QVQLVQSGAEVKKPGSSVKVSCKASGYAFT**SYWMH**WVRQAPGQGLEWMG**QINPT**
TGRSOYNEKFKTRVTTITADKSTSTAYMELSSLRSEDTAVYYCAR**WGLOPFAY**WGQ
25 GTLVTVSS (SEQ ID NO: 4),

and the light chain variable region comprises the amino acid sequence of
DIQMTQSPSFLSASVGDRVTTITC**KASQDVSTAVA**WYQQKPGKAPKLLIY**SASYRYT**
GVPSRFGSGSGTDFTLTISLQPEDFATYYC**QOHYSTPW**TFGGGTKVEIK (SEQ ID
NO: 10).

17. The method of any one of claims 1-15, wherein the antibody, or antigen binding portion thereof, comprises an Fc domain which comprises an amino acid sequence selected from:

5 EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPG (SEQ ID NO: 13 ; IgG1-P238K (-C-term Lys)),

10 EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK
VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH
YTQKSLSLSPGK (SEQ ID NO: 14; IgG1-P238K),

15 *ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL*
*QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCDKTHTCPPCPAPELL
GGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFF
20 LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 15; CH1-
IgG1-P238K (-C-term Lys)),

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
*QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV*EPKSCDKTHTCPPCPAPELL
GGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
25 REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFF
LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 16;
CH1-IgG1-P238K),

EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
30 DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT

QKSLSLSPG (SEQ ID NO: 17; IgG1f-P238K (-C-term Lys)),

EPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW
5 ESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 18; IgG1f-P238K),

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL
GGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
10 REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 19;
CH1-IgG1f-P238K (-C-term Lys)),

or

15 ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELL
GGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ
VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSF
20 FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID No: 20;
CH1-IgG1f-P238K).

18. The method of any one of claims 1-17, wherein the antibody, or antigen
binding portion thereof wherein the first polypeptide portion comprises or consists of an
25 amino acid sequence of

QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMG
QINPTTGRSOYNEKEFKTRVTITADKSTSTAYMELSSLRSEDVAVYYCAR**WGLOPE**
AYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
30 CPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP

PVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K - no terminal lysine); and

the second polypeptide portion comprises or consists of the amino acid sequence of
 DIQMTQSPSFLSASVGDRVITITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYT
 5 GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQOHYSTPWTFGGGTKVEIKRTVAAPS
 VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
 SSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11; LC_Y12XX-hz28-CL).

10 19. The method of any one of claims 1-18, wherein the antibody, or antigen binding portion thereof, is antibody BMS-986325, wherein the first polypeptide portion has the amino acid sequence of

QVQLVQSGAEVKKPGSSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMG
QINPTTGRSOYNEKEFKTRVTITADKSTSTAYMELSSLRSEDVAVYYCARWGLOPF
 15 AYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
 SGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
 CPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
 EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
 AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTP
 20 PVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K - no terminal lysine); and

the second polypeptide portion has the amino acid sequence of
 DIQMTQSPSFLSASVGDRVITITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYT
 GVPSRFSGSGSGTDFTLTISLQPEDFATYYCQOHYSTPWTFGGGTKVEIKRTVAAPS
 25 VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
 SSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11; LC_Y12XX-hz28-CL).

20. A kit for treating an autoimmune disease such as Sjögren's Syndrome in a
 30 human patient, the kit comprising:

(a) a dose of antibody BMS-986325, wherein the first polypeptide portion has the amino acid sequence of

QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMG
QINPTTGRSOYNEKEFKTRVTITADKSTSTAYMELSSLRSED~~T~~AVYYCARWGLOPF
 5 AYWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT
 SGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHT
 CPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
 EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
 AKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPP
 10 PVLDSGDGSFFLYSKLTVDKSRWQQGNVFSQSVMSHEALHNHYTQKSLSLSPG (SEQ ID
 NO: 5; HC_Y12XX-hz28-CH1-IgG1-P238K- no terminal lysine); and

the second polypeptide portion has the amino acid sequence of
 DIQMTQSPSFSLASVGDRTITTCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYT
 GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQOHYSTPWTFGGGTKVEIKRTVAAPS
 15 VFIFPPSDEQLKSGTASVVCLLNNFYPRKAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
 SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 11; LC_Y12XX-
 hz28-CL), and

(b) instructional material for using the antibody in the method of any one of claims 1-19.

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21. The kit of claim 20, wherein the dose of antibody BMS-986325 ranges from 0.3 milligram (mg) to 1000 mg.

22. The kit of claim 20 or 21, wherein the dose of antibody BMS-986325 is a
 25 formulation comprising 20 mM histidine, 250 mM sucrose, 50 micromolar pentetic acid and 0.05% (w/v) polysorbate 80, pH 6.0.