

III. SUMMARY

[0008a] In one aspect, the present disclosure relates to use of a soluble B-cell maturation antigen (sBCMA) variant-Fc fusion protein in the manufacture of a medicament for reducing production of IgA, IgM and/or IgG in a subject diagnosed with an autoimmune disease or fibrosis, wherein the sBCMA variant-Fc fusion protein comprises: a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index; b) an optional linker; and c) an Fc domain.

[0009] The present disclosure provides *inter alia*, a method of reducing immunoglobulin production in a subject diagnosed with an autoimmune disease and/or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant protein and/or sBCMA variant -Fc fusion protein. In some examples, the present disclosure provides *inter alia*, a method of reducing immunoglobulin production in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some examples, the present disclosure provides *inter alia*, a method of reducing immunoglobulin production in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant -Fc fusion protein. In some examples, the present disclosure provides *inter alia*, a method of reducing immunoglobulin production in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some examples, the present disclosure provides *inter alia*, a method of reducing immunoglobulin production in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant-Fc fusion protein.

[0010] The present disclosure provides *inter alia*, a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease and/or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant protein and/or sBCMA variant -Fc fusion protein. In some examples, the present disclosure provides *inter alia*, a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease, said method comprising

administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some examples, the present disclosure provides *inter alia*, a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant -Fc fusion protein. In some examples, the present disclosure provides *inter alia*, a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant protein. In some examples, the present disclosure provides *inter alia*, a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with fibrosis, said method comprising administering to the subject a therapeutically effective dose of an sBCMA variant-Fc fusion protein. In some examples, the method as disclosed herein reduces production of IgA. In some examples, the method as disclosed herein reduces production of IgM. In some examples, the method as disclosed herein reduces production of IgG. In some examples, the method as disclosed herein reduces production of both IgA and IgM. In some examples, the method as disclosed herein reduces production of both IgA and IgG. In some examples, the method as disclosed herein reduces production of both IgM and IgG. In some examples, the method as disclosed herein reduces production of IgA, IgM and IgG.

[0011] In one example, the disclosure provides a method of reducing production of IgA, IgM, and/or IgG in a subject diagnosed with an autoimmune disease or fibrosis, said method comprising administering to the subject a therapeutically effective dose of a soluble B-cell maturation antigen (sBCMA) variant-Fc fusion protein, wherein the sBCMA variant-Fc fusion protein comprises:

a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index;

b) an optional linker; and

c) an Fc domain.

[0012] In an additional example, the disclosure provides the method as disclosed herein, wherein normal B cell viability is not altered.

[0013] In a further example, the disclosure provides the method as disclosed herein, wherein the method reduces production of IgA.

[0014] In an additional example, the disclosure provides the method as disclosed herein, wherein the method reduces production of IgM.

[0015] In a further example, the disclosure provides the method as disclosed herein, wherein the method reduces production of IgG.

[0016] In a further example, the disclosure provides the method as disclosed herein, wherein the method reduces production of both IgA and IgM.

[0017] In a further example, the disclosure provides the method as disclosed herein, wherein the method reduces production of both IgA and IgG.

[0018] In a further example, the disclosure provides the method as disclosed herein, wherein the method reduces production of both IgM and IgG.

[0019] In a further example, the disclosure provides the method as disclosed herein, wherein the method reduces production of IgA, IgM and IgG.

[0020] In a further example, the disclosure provides the method as disclosed herein, wherein the subject is diagnosed with the autoimmune disease.

[0021] In an additional example, the disclosure provides the method as disclosed herein, wherein the autoimmune disease is selected from the group consisting of IgA Nephropathy, Systemic Lupus Erythematosus, Churg-Strauss Syndrome, Myasthenia Gravis, Multiple Sclerosis, and rheumatoid arthritis. In an additional example, the disclosure provides the method as disclosed herein, wherein the autoimmune disease is Lupus.

[0022] In a further example, the disclosure provides the method as disclosed herein, wherein the subject is diagnosed with the fibrosis.

[0023] In an additional example, the disclosure provides the method as disclosed herein, wherein the fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis, non-alcoholic steatohepatitis, scleroderma, and kidney fibrosis.

[0024] In a further example, the disclosure provides the method as disclosed herein, wherein said fusion protein comprises, from N- to C-terminal:

- a) said variant sBCMA domain;
- b) said optional linker; and
- c) said Fc domain.

[0025] In a further example, the disclosure provides the method as disclosed herein, wherein said fusion protein comprises, from N- to C-terminal:

- a) said Fc domain;
- b) said optional linker; and
- c) said variant sBCMA domain.

[0026] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

[0027] In a further example, the disclosure provides the method as disclosed herein, wherein said amino acid substitution(s) occur at one of said positions, two of said positions, three of said positions, four of said positions, five of said positions, six of said positions, seven of said positions, eight of said positions, or nine of said positions.

[0028] In an additional example, the disclosure provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0029] In a further example, the disclosure provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

[0030] In an additional example, the disclosure provides the method as disclosed herein, wherein said amino acid substitution(s) is selected from the group consisting of S16G, H19Y and T36A.

[0031] In a further example, the disclosure provides the method as disclosed herein, wherein said amino acid substitutions are selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G, H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A, H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T, S16G/H19Y/S44N/K50R, N11D/H19Y/S48T, S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R, H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A, M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D, M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S, M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D, M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D, S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R, S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M, M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R, M1T/A5T/S9P/S16G/Q25R/N31D/V49M, L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A, G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M,

N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D, S9P/N11D/S16G/H19Y/T36A/N47S/N53D, Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M, M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S, M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K, M1T/N11D/H19Y/T36A/N42S/V45A/N53S, M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E, M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

[0032] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0033] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[0034] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

[0035] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0036] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain comprises the amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

[0037] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 67.

[0038] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 68.

[0039] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 69.

[0040] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 49.

[0041] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 74.

[0042] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 67.

[0043] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 68.

[0044] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 69.

[0045] In a further example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 49.

[0046] In an additional example, the disclosure provides the method as disclosed herein, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 74.

[0047] In a further example, the disclosure provides the method as disclosed herein, wherein said Fc domain is a human IgG Fc domain or a variant human IgG Fc domain.

[0048] In an additional example, the disclosure provides the method as disclosed herein, wherein said human IgG Fc domain comprises the hinge-CH2-CH3 of human IgG1.

[0049] In a further example, the disclosure provides the method as disclosed herein, wherein said Fc domain is a variant human IgG Fc domain.

[0050] In an additional example, the disclosure provides the method as disclosed herein, wherein said Fc domain is a human IgG1 Fc domain.

[0051] In a further example, the disclosure provides the method as disclosed herein, wherein said linker is SEQ ID NO:87.

[0052] In an additional example, the disclosure provides the method as disclosed herein, wherein said linker is selected from the group consisting of (GS)_n, (GSGGS)_n, (GGGGS)_n, and (GGGS)_n, wherein n is selected from the group consisting of 1, 2, 3, 4 and 5.

[0053] In a further example, the disclosure provides the method as disclosed herein, wherein said linker is SEQ ID NO:88.

[0054] In an additional example, the disclosure provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:80.

[0055] In a further example, the disclosure provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:81.

[0056] In an additional example, the disclosure provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:82.

[0057] In a further example, the disclosure provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:83.

[0058] In an additional example, the disclosure provides the method as disclosed herein, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:84.

IV. BRIEF DESCRIPTION OF THE DRAWINGS

[0059] **Figure 1** shows nonhuman single dose toxicity study design.

[0060] **Figure 2** shows immune cell counts in male cynomolgus monkeys in single dose toxicity studies treated with vehicle control and variant sBCMA Fc at 0.1mg/kg, 1mg/kg, 10mg/kg and 100mg/kg. **Figure 2A**, CD3+CD4+ T Lymphocyte. **Figure 2B**,

5. Linkers

[00283] The fusion proteins of the invention can include optional linkers to connect the sBCMA domain to the Fc domain.

[00284] By “linker” or “linker peptide” as used herein have a length that is adequate to link two molecules in such a way that they assume the correct conformation relative to one another so that they retain the desired activity. In one embodiment, the linker is from about 1 to 20 amino acids in length, preferably about 1 to 10 amino acids in length. In one embodiment, linkers of 4 to 10 amino acids in length may be used. Useful linkers include IEGRMD or glycine- serine polymers, including for example (GS)_n, (GSGGS)_n (SEQ ID NO. 89), (GGGGS)_n (SEQ ID NO.90), and (GGGS)_n (SEQ ID NO. 91), where n is an integer of at least one (and generally from 3 to 4), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers. Alternatively, a variety of nonproteinaceous polymers, including but not limited to polyethylene glycol (PEG), polypropylene glycol, polyoxyalkylenes, or copolymers of polyethylene glycol and polypropylene glycol, may find use as linkers.

[00285] In some embodiments, the linker is a "domain linker", used to link any two domains as outlined herein together, such as to link the variant sBCMA domain with Fc domain. As discussed above, many suitable linkers can be used to allow for recombinant attachment of the two domains with sufficient length and flexibility to allow each domain to retain its biological function. As discussed herein, a particularly useful domain linker is an IEGRMD linker joined to the hinge domain of IgG1.

[00286] In various embodiments, two domains (*e.g.* the sBCMA variant domain and the Fc domain) are generally linked using a domain linker as described herein. In many embodiments, two domains are attached using a flexible linker in such a way that the two domains can act independently. Flexible linkage can be accomplished in a variety of ways, using traditional linkers and/or the hinge linker.

[00287] In some embodiments, the linker as described herein is IEGRMD (SEQ. ID NO. 87).

[00288] In some embodiments, the linker as described herein is GGGGS (SEQ. ID NO. 88).

WHAT IS CLAIMED IS:

1. Use of a soluble B-cell maturation antigen (sBCMA) variant-Fc fusion protein in the manufacture of a medicament for reducing production of IgA, IgM and/or IgG in a subject diagnosed with an autoimmune disease or fibrosis, wherein the sBCMA variant-Fc fusion protein comprises:

a) a variant sBCMA domain comprising at least one amino acid substitution as compared to SEQ ID NO:1, wherein said amino acid substitution is at a position number selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 16, 19, 20, 22, 23, 25, 26, 29, 31, 32, 35, 36, 38, 39, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, and 54, wherein the numbering is according to the EU index;

b) an optional linker; and

c) an Fc domain.

2. The use according to claim 1, wherein normal B cell viability is not altered.

3. The use according to claim 1 or claim 2, wherein the medicament reduces production of IgA.

4. The use according to claim 1 or claim 2, wherein the medicament reduces production of IgM.

5. The use according to claim 1 or claim 2, wherein the medicament reduces production of IgG.

6. The use according to claim 1 or claim 2, wherein the medicament reduces production of both IgA and IgM.

7. The use according to claim 1 or claim 2, wherein the medicament reduces production of both IgA and IgG.

8. The use according to claim 1 or claim 2, wherein the medicament reduces production of both IgM and IgG.

9. The use according to claim 1 or claim 2, wherein the medicament reduces production of IgA, IgM and IgG.
10. The use according to any one of the preceding claims, wherein the subject is diagnosed with the autoimmune disease.
11. The use according to claim 10, wherein the autoimmune disease is selected from the group consisting of IgA Nephropathy, Systemic Lupus Erythematosus, Churg-Strauss Syndrome, Myasthenia Gravis, Multiple Sclerosis, and rheumatoid arthritis.
12. The use according to any one of the preceding claims, wherein the subject is diagnosed with the fibrosis.
13. The use according to claim 12, wherein the fibrosis is selected from the group consisting of idiopathic pulmonary fibrosis, non-alcoholic steatohepatitis, scleroderma, and kidney fibrosis.
14. The use according to any one of the preceding claims, wherein said fusion protein comprises, from N- to C-terminal:
 - a) said variant sBCMA domain;
 - b) said optional linker; and
 - c) said Fc domain.
15. The use according to any one of claims 1-13, wherein said fusion protein comprises, from N- to C-terminal:
 - a) said Fc domain;
 - b) said optional linker; and
 - c) said variant sBCMA domain.
16. The use according to any one of the preceding claims, wherein said variant sBCMA domain has at least 80%, at least 85%, at least 90%, or at least 95% sequence identity to SEQ ID NO:1.

17. The use according to any one of the preceding claims, wherein said amino acid substitution(s) occur at one of said positions, two of said positions, three of said positions, four of said positions, five of said positions, six of said positions, seven of said positions, eight of said positions, or nine of said positions.

18. The use according to any one of the preceding claims, wherein said amino acid substitution(s) is selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36A, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

19. The use according to any one of the preceding claims, wherein said amino acid substitution(s) is selected from the group consisting of M1V, L2S, Q3P, M4T, S9P, N11D, S16G, H19Y, N31S, N31D, T32I, T36A, R39H, N47S, K50E, and N53E.

20. The use according to any one of the preceding claims, wherein said amino acid substitution(s) is selected from the group consisting of S16G, H19Y and T36A.

21. The use according to any one of claims 1-18, wherein said amino acid substitutions are selected from the group consisting of L2S/S9P/E12K/N31D/T36A/N42S/N53S, M1V/T32P/T36A/T46I/N53D/A54V, Q3R/S16N/T36A/A43T, F14L/S16G/T36A/V45A/N47D, M1T/M4V/S9F/S16G/T32A/Q38R, M1A/S9A/Q38R, G6E/Q25R/Q38R, M1V/M4I/G6E/S9P/N11D/V49M/T52M/A54V, N11D/S16G/N31S, N11D/H19Y/I22M/T32P/N47S/N53S, G6E/Q7R/H19Y/L35S, H19Y/N42D/S48P/T52A, M1V/N31D/T32I/T36A, M1V/A5T/H19L/T36A, M1T/N31D/T32A/T36A/Q38R/S44D/V49A/K50E, M1V/T36A/Q38R/A43V, M1V/L2S/S9P/Q10H/T36A/Q38R/K50G, T36A/Q38R/N53S, M1T/L2S/L35P/T36A/Q38R/T46A/K50R, A5T/A20V/T36A/Q38R, M1T/S16G/I22V/T36A/S44G/T46A/V49A, S16G/T36A, M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R, M1C/L2C/Q3R/M4E/N11D/S16G/T36P,

M1I/N11D/S16G/I22M/S29A/T36A/S44G/K50R,
N11D/N31D/T32I/T36A/S44N/N47D/N53D, M1R/L2C/Q3R, H19Y/T36A/S44G,
H19Y/T32I/T36A/V49A, H19Y/N31S/T36A/V45A, H19Y/N31S/T36A, H19Y/T36P/T52A,
H19Y/N31D/T52M, M1V/H19Y/V45M, S16G/H19Y/N47D, S16G/H19Y/K50T,
S16G/H19Y/S44N/K50R, N11D/H19Y/S48T,
S9P/N11D/S16R/T32A/Q38R/S44G/T46I/T52A/N53D/A54T, N11D/S16G/S44R,
H19L/T32A/S44G/G51E/T52A, S16N/H19Y/T36A/K50R, M1V/H19Y/T36A/R39H/T46A,
M1V/H19Y/T36A, H19Y/T36A/N42D/N47S/S48P, M1V/H19Y/T36A/S44G/N47D,
M1V/H19Y/T36A/N42R/N53S, H19Y/L35P/T36A/N42D/T46I/V49A,
Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/H19Y/T36A/N42R/N53S,
M1T/H19Y/T36A, M1V/S16N/H19Y/I22M/T36A,
M1T/N11D/H19Y/T36A/N42S/V45A/N53S, N11D/S16G/H19Y/T36A/N47S/N53D,
M1V/S9P/Q10P/S16G/H19Y/L26F/T36A/A43V/N53D, S16G/H19Y/T36A/V49A/N53D,
S16G/T36A/A43T/S44G/V45M, M4V/S9P/S16G/T36A/Q38R,
S9P/N11S/S16G/T36A/Q38R, N11D/E12K/S16R/T36A/T52M,
M4V/T32I/T36A/Q38R/A43T/V45A/S48P, S9P/N11D/S16G/Q25R,
M1T/A5T/S9P/S16G/Q25R/N31D/V49M,
L2S/S9P/S16G/A20T/T32I/Q38R/N42D/T46A/S48L, S16G/Q25R/T46A,
G6E/S9A/S16G/Q25R/N31D/N47S/T52M, H19Y/Q38R/T52M,
N11D/H19Y/I22M/T32P/N47S/N53S, S16G/H19Y/T36A, S16G/H19Y/T36A/N53D,
S9P/N11D/S16G/H19Y/T36A/N47S/N53D,
Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, M1V/L2S/M4T/N11D/H19Y/T36A,
M1V/L2S/M4T/N11D/T36A, M1V/L2S/M4T/H19Y/T36I/V45A/V49M,
M1V/L2S/M4T/N11D/H19Y/T36A, M1V/L2S/M4T/S9P/Q10R/H19Y/T36A/T46A/N47S,
M1V/L2S/M4T/S16G/N31D/T32I/T36A, M1V/M4T/T36A/Q38R/N53K,
M1T/N11D/H19Y/T36A/N42S/V45A/N53S,
M1T/N31D/T32A/T36A/A38R/S44D/V49A/K50E,
M1T/S9P/P23S/Q38R/N42S/S48P/V49A/A54V, H19Y/T36A/S44G, H19Y/T36A, and
M4T/T36A/Q38R/N42S/S44G/T46A/N47K/S48P/T52A.

22. The use according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H,

Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

23. The use according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions S16G/H19Y/T36A/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

24. The use according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions S9P/N11D/S16G/H19Y/T36A/N47S/N53D, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3P, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11S, E12K, F14L, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, N31S, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53K, N53S, A54V, and A54T.

25. The use according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions Q3P/S9P/H19Y/N31S/T36A/R39H/N47R/K50E, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, M1V, L2C, L2S, Q3R, M4E, M4I, M4T, M4V, A5T, G6E, Q7R, S9A, S9F, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16G, S16N, S16R, H19L, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31D, T32A, T32I, T32P, L35S, L35P, T36I, T36P, Q38R, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M,

T46A, T46I, N47D, N47K, N47S, S48L, S48P, S48T, V49A, V49M, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

26. The use according to any one of claims 1-18, wherein said variant sBCMA domain comprises the amino acid substitutions M1V/L2S/M4T/S16G/N31D/T32I/T36A, and at least one further amino acid substitution selected from the group consisting of M1A, M1C, M1I, M1R, M1T, L2C, Q3P, Q3R, M4E, M4I, M4V, A5T, G6E, Q7R, S9A, S9F, S9P, Q10H, Q10P, Q10R, N11D, N11S, E12K, F14L, S16N, S16R, H19L, H19Y, A20V, A20T, I22M, I22V, P23S, Q25R, L26F, S29A, N31S, T32A, T32P, L35S, L35P, T36I, T36P, Q38R, R39H, N42D, N42R, N42S, A43T, A43V, S44D, S44G, S44N, S44R, V45A, V45M, T46A, T46I, N47D, N47K, N47R, N47S, S48L, S48P, S48T, V49A, V49M, K50E, K50G, K50R, K50T, G51E, T52A, T52M, N53D, N53K, N53S, A54V, and A54T.

27. The use according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 67.

28. The use according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 68.

29. The use according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 69.

30. The use according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 49.

31. The use according to any one of claims 1-18, wherein said variant sBCMA domain has at least 90% sequence identity to SEQ ID NO: 74.

32. The use according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 67.

33. The use according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 68.

34. The use according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 69.
35. The use according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 49.
36. The use according to any one of claims 1-18, wherein said variant sBCMA domain has the amino acid sequence of SEQ ID NO: 74.
37. The use according to any one of the preceding claims, wherein said Fc domain is a human IgG Fc domain or a variant human IgG Fc domain.
38. The use according to claim 37, wherein said human IgG Fc domain comprises the hinge-CH2-CH3 of human IgG1.
39. The use according to claim 37, wherein said Fc domain is a variant human IgG Fc domain.
40. The use according to claim 37, wherein said Fc domain is a human IgG1 Fc domain.
41. The use according to any one of the preceding claims, wherein said linker is SEQ ID NO:87.
42. The use according to any one of claims 1-40, wherein said linker is selected from the group consisting of (GS)_n, (GSGGS)_n, (GGGGS)_n, and (GGGS)_n, wherein n is selected from the group consisting of 1, 2, 3, 4 and 5.
43. The use according to claim 42, wherein said linker is SEQ ID NO:88.
44. The use according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:80.
45. The use according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:81.

46. The use according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:82.

47. The use according to claim 1 or claim 2, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:83.

48. The use according to any one of claims 1-4, wherein the sBCMA variant – Fc fusion protein comprises the amino acid sequence of SEQ ID NO:84.