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(54) **Title:** ANTIBODY FORMULATION

(57) **Abstract:** Anti-BAFFR antibodies are formulated as lyophilisate or liquid formulation. The lyophilisates can be reconstituted to give a solution with a high concentration of the antibody active ingredient for delivery to a patient without high levels of antibody aggregation. The lyophilisate can be reconstituted with an aqueous reconstituent to provide an aqueous composition in which the antibody has a concentration of at least 50mg/ml. The lyophilisate or aqueous pharmaceutical composition may include one or more of a sugar, a buffering agent, a surfactant, and/or a free amino acid.

ANTIBODY FORMULATION

Technical Field

The present invention relates to a pharmaceutical formulation of an antibody against BAFFR (BAFF receptor), a process for the preparation thereof and uses of the
5 formulation.

Background

The BAFFR:BAFF pair is critically involved in the maturation of transitional B-cells, for survival and activation of mature B-cells, and for isotype class switching in response to T cell-dependent antigens. BAFF and its receptor BAFFR are also important for survival
10 and growth of malignant B-cells. Further, BAFFR normally is not expressed on pre-B cells, but was recently shown to be expressed on human ALL (B-lineage acute lymphoblastic leukemia) cells (Parameswaran, 2010, Cancer Res. 70(11) 4346-4356). The removal of autoreactive B cells and the blockade of inappropriate survival/activation mediated by excess BAFF levels in patients suffering from autoimmune disorders or
15 cancer represents a well-validated therapeutic goal. Thus, an anti-BAFFR antibody, in particular an antibody capable of antibody-dependent cell-mediated cytotoxicity (ADCC) and blockade of ligand binding to BAFFR may offer an effective therapeutic agent in autoimmune diseases and B cell neoplasms.

Antibodies against BAFFR are known from e.g. WO 2010/007082 and include antibodies
20 which are characterized by comprising a V_H domain with the amino acid sequence of SEQ ID NO: 1 and a V_L domain with the amino acid sequence of SEQ ID NO: 2. The antibody MOR6654 is one such antibody (IgG1 kappa). It has the heavy chain amino acid sequence of SEQ ID NO: 9 and the light chain amino acid sequence of SEQ ID NO: 10. This antibody may be expressed from SEQ ID NOs: 14 and 15, preferably in a host
25 cell which lacks fucosyl-transferase, for example in a mammalian cell line with an inactive FUT8(-/-) gene, to give a functional non-fucosylated anti-BAFFR antibody with enhanced ADCC. This antibody is referred to hereafter as MOR6654B. Alternative ways to produce non-fucosylated antibodies are known in the art.

Formulations with high concentration of antibody may have short shelf lives and the
30 formulated antibodies may lose biological activity resulting from chemical and physical instabilities during the storage. Among those, aggregation, deamidation and oxidation are known to be the most common causes of antibody degradation. In particular, aggregation can potentially lead to increased immune response in patients, leading to safety concerns. Thus it must be minimized or prevented.

It is an object of the invention to provide further and improved formulations of anti-BAFFR antibodies, and in particular formulations with high concentration of anti-BAFFR antibodies and low levels of antibody aggregation.

Disclosure of the invention

5 Therapeutic antibodies are typically formulated either in aqueous form ready for parenteral administration or as lyophilisates for reconstitution with a suitable diluent prior to administration. According to the invention, an anti-BAFFR antibody may be formulated either as a lyophilisate, or as an aqueous composition, for example in pre-filled syringes. Suitable formulation can provide an aqueous pharmaceutical composition or a
10 lyophilisate which can be reconstituted to give a solution with a high concentration of the antibody active ingredient and a low level of antibody aggregation for delivery to a patient. High concentrations of antibody are useful as they reduce the amount of material which must be delivered to a patient. Reduced dosing volumes minimize the time taken to deliver a fixed dose to the patient. The aqueous compositions of the invention with
15 high concentration of anti-BAFFR antibodies are particularly suitable for subcutaneous administration.

Thus the invention provides an aqueous pharmaceutical composition, suitable for parenteral administration in a subject, e.g., for subcutaneous administration, comprising an anti-BAFFR antibody.

20 The following specific embodiments of the invention are described as numbered hereafter:

1. An aqueous pharmaceutical composition, suitable for subcutaneous administration in a subject, comprising an anti-BAFFR antibody in which the antibody has a concentration of at least 50mg/ml, and wherein said anti-BAFFR antibody includes:
25 (i) one or more heavy chain CDRs selected from the group consisting of SEQ ID NOs: 3, 4 and 5; and/or (ii) one or more light chain CDRs selected from the group consisting of SEQ ID NOs: 6, 7 and 8.
2. The aqueous pharmaceutical composition, suitable for subcutaneous administration in a subject, according to Embodiment 1, wherein said anti-BAFFR antibody includes
30 heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8.
3. The aqueous pharmaceutical composition of Embodiment 1 or 2, wherein the anti-BAFFR antibody comprises a V_H domain with amino acid SEQ ID NO: 1 and a V_L domain with amino acid SEQ ID NO: 2.

4. The aqueous pharmaceutical composition of Embodiment 1, 2 or 3, wherein the anti-BAFFR antibody comprises a heavy chain region of SEQ ID NO: 9 and a light chain region of SEQ ID NO: 10.
5. The aqueous pharmaceutical composition of any one of Embodiments 1 to 4,
5 wherein less than 5% of the anti-BAFFR antibody is aggregated or degraded.
6. The aqueous pharmaceutical composition of any one of Embodiments 1 to 5, comprising one or more of the following components selected among the group consisting of: a stabilizer, a buffering agent; and a surfactant.
7. The aqueous pharmaceutical composition of Embodiment 6, wherein the stabilizer is
10 a sugar.
8. The aqueous pharmaceutical composition of Embodiment 6 or 7, comprising: a sugar, a buffering agent, and a surfactant.
9. The aqueous pharmaceutical composition of Embodiment 6 or 7, further comprising a free amino acid.
- 15 10. The aqueous pharmaceutical composition of Embodiment 7 to 9, comprising sucrose as a sugar.
11. The aqueous pharmaceutical composition of Embodiment 10, comprising 200-300 mM sucrose.
12. The aqueous pharmaceutical composition of Embodiments 6-11, comprising a
20 histidine buffer as the buffering agent.
13. The aqueous pharmaceutical composition of Embodiment 12, comprising 25-35 mM histidine buffer.
14. The aqueous pharmaceutical composition of Embodiments 6 to 13, comprising polysorbate 80 as a surfactant.
- 25 15. The aqueous pharmaceutical composition of Embodiment 14, comprising 0.01 to 0.1% polysorbate 80.
16. The aqueous pharmaceutical composition of Embodiment 9, further comprising arginine as free amino acid.
17. The aqueous pharmaceutical composition of Embodiment 16, comprising 40-80 mM
30 arginine.
18. The aqueous pharmaceutical composition of any preceding Embodiment, comprising sucrose, a histidine buffer, polysorbate 80 and arginine.

19. A lyophilisate suitable for preparing the aqueous pharmaceutical composition of any preceding Embodiments.
20. A lyophilisate according to Embodiment 19, comprising sucrose, a histidine buffer, polysorbate 80 and arginine.
- 5 21. A method for preparing a lyophilisate, comprising the steps of: (i) preparing an aqueous solution comprising an anti-BAFFR antibody, a sugar, a buffering agent, a surfactant and optionally a free amino acid; and (ii) lyophilizing the aqueous solution.
22. A delivery device including the aqueous pharmaceutical composition of any one of Embodiments 1-18.
- 10 23. A pre-filled syringe including the aqueous pharmaceutical composition of any one of Embodiments 1-18.
24. A method for delivering an anti-BAFFR monoclonal antibody to a mammal, comprising a step of administering to the patient a pharmaceutical composition of any one of Embodiments 1-18.
- 15 25. The composition of any one of Embodiments 1-18, for use in treating a disease or disorder that is mediated by BAFF receptor or that can be treated by killing or depleting B cells.
26. The composition of Embodiment 25, for the treatment of autoimmune diseases.
27. The composition of Embodiment 25, for the treatment of B cell neoplasms, such as
20 lymphoma, leukemia or myeloma.
28. The composition of Embodiment 26, for the treatment of rheumatoid arthritis, systemic lupus erythematosus, or Pemphigus vulgaris.
29. The aqueous pharmaceutical composition of any one of Embodiments 1-18 in which
25 the antibody has a concentration of at least at least 50mg/ml, at least 100mg/ml, at least 150mg/ml, at least 200mg/ml, at least 250mg/ml, or at least 300mg/ml.
- The invention also provides an aqueous pharmaceutical composition comprising: an anti-BAFFR monoclonal antibody as described above, for example MOR6654, especially MOR6654B; a stabilizer; a buffering agent; and a surfactant. The composition preferably also includes a free amino acid.
- 30 The invention also provides a lyophilisate comprising: an anti-BAFFR monoclonal antibody as described above, for example MOR6654, especially, MOR6654B; a sugar; a buffering agent; and a surfactant. The lyophilisate preferably also includes a free amino acid.

The invention also provides a lyophilisate comprising an anti-BAFFR monoclonal antibody as described above, for example MOR6654, especially, MOR6654B, wherein the lyophilisate can be reconstituted with an aqueous reconstituent to provide an aqueous composition in which the antibody has a concentration of at least 50mg/ml, 100mg/ml, 150mg/ml, 200mg/ml, 250mg/ml, or 300mg/ml, after reconstitution in an aqueous solution.

The invention also provides an aqueous pharmaceutical composition comprising high concentration of an anti-BAFFR monoclonal antibody as described above, for example MOR6654, especially, MOR6654B, wherein less than 5%, 4%, 3%, 2% or 1% of the anti-BAFFR antibody is aggregated or degraded.

The invention also provides a process for preparing a lyophilisate, comprising steps of: (i) preparing an aqueous solution comprising an anti-BAFFR monoclonal antibody, a sugar, a buffering agent, a surfactant, and optionally a free amino acid; and (ii) lyophilizing the aqueous solution.

The invention also provides a process for preparing a pharmaceutical composition, comprising a step of mixing a lyophilisate with an aqueous reconstituent, wherein the lyophilisate comprises an anti-BAFFR monoclonal antibody, a sugar, a buffering agent, a surfactant, and optionally a free amino acid.

More specifically the invention provides a lyophilized formulation prepared by lyophilizing an aqueous formulation having a pH of 5.0-7.0 and comprising

(i) an anti-BAFFR antibody wherein the antibody has a concentration of 20-120 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,

(ii) a stabilizer,

(iii) a buffering agent,

(iv) a surfactant, and optionally

(v) an amino acid.

In one embodiment said lyophilized formulation is prepared from an aqueous formulation having a pH of 5.0-7.0 and comprising

(i) an anti-BAFFR antibody wherein the antibody has a concentration of 20-120mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,

- (ii) sucrose or trehalose as a stabilizer,
 - (iii) histidine as a buffering agent,
 - (iv) polysorbate 80 as a surfactant, and optionally
 - (v) an amino acid selected from arginine and glycine.
- 5 In one embodiment said lyophilized formulation is prepared from an aqueous formulation having a pH of 5.0-7.0 and comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 20-120 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 10
- (ii) 3-300 mM sucrose or trehalose as a stabilizer,
 - (iii) 1-60 mM histidine as a buffering agent,
 - (iv) up to 0.2% polysorbate 80 as a surfactant, and optionally
 - (v) 2-80 mM arginine or glycine.
- 15 In one embodiment said lyophilized formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 20
- (ii) 90 mM sucrose as a stabilizer,
 - (iii) 7 mM histidine as a buffering agent, and
 - (iv) 0.02% polysorbate 80 as a surfactant.
- In one embodiment said lyophilized formulation is prepared from an aqueous formulation
- 25 having a pH of 6.5 and comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 30
- (ii) 90 mM sucrose as a stabilizer,
 - (iii) 7 mM histidine as a buffering agent,

- (iv) 0.02% polysorbate 80 as a surfactant, and
- (v) 20 mM glycine-HCl.

In one embodiment said lyophilized formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising

- 5 (i) an anti-BAFFR antibody wherein the antibody has a concentration of 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) 90 mM sucrose as a stabilizer,
- 10 (iii) 7 mM histidine as a buffering agent,
- (iv) 0.02% polysorbate 80 as a surfactant, and
- (v) 17 mM arginine-HCl.

In one embodiment said lyophilized formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising

- 15 (i) an anti-BAFFR antibody wherein the antibody has a concentration of 66.6 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) 90 mM sucrose as a stabilizer,
- 20 (iii) 7 mM histidine as a buffering agent,
- (iv) 0.02% polysorbate 80 as a surfactant, and
- (v) 17 mM arginine-HCl.

The invention also provides an aqueous pharmaceutical composition obtained by reconstituting a lyophilized formulation as described above, wherein the reconstitution factor is between 1:0.5 to 1:6. A reconstitution factor of 1:3 is useful.

The invention also provides an aqueous pharmaceutical composition having a pH of 5.0 to 7.0 comprising

- 30 (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) a stabilizer,

- (iii) a buffering agent,
- (iv) a surfactant, and optionally
- (v) an amino acid.

5 In one embodiment the aqueous pharmaceutical composition having a pH of 5.0 to 7.0 comprises

- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 10 (ii) sucrose or trehalose as a stabilizer,
- (iii) histidine as a buffering agent,
- (iv) polysorbate 80 as a surfactant, and optionally
- (v) an amino acid selected from arginine and glycine.

15 In one embodiment the aqueous pharmaceutical composition having a pH of 5.0 to 7.0 comprises

- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 20 (ii) 200-300 mM sucrose as a stabilizer,
- (iii) 25-35 mM histidine as a buffering agent,
- (iv) up to 0.2% polysorbate 80 as a surfactant, and optionally
- (v) 10-80 mM arginine or glycine.

25 In one embodiment the aqueous pharmaceutical composition has a pH of 6.5 and comprises

- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 30 (ii) 270 mM sucrose as a stabilizer,
- (iii) 21 mM histidine as a buffering agent, and

(iv) 0.06% polysorbate 80 as a surfactant.

In one embodiment the aqueous pharmaceutical composition has a pH of 6.5 and comprises

5 (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,

(ii) 270 mM sucrose as a stabilizer,

(iii) 21 mM histidine as a buffering agent,

10 (iv) 0.06% polysorbate 80 as a surfactant, and

(v) 60 mM glycine.

In one embodiment the aqueous pharmaceutical composition has a pH of 6.5 and comprises

15 (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,

(ii) 270 mM sucrose as a stabilizer,

(iii) 21 mM histidine as a buffering agent,

20 (iv) 0.06% polysorbate 80 as a surfactant, and

(v) 51 mM arginine.

In one embodiment the aqueous pharmaceutical composition of the invention has a BAFFR antibody concentration of 150 mg/ml.

25 In one embodiment the lyophilized formulation or the aqueous pharmaceutical composition of the invention comprises an anti-BAFFR antibody comprising a V_H domain with amino acid SEQ ID NO: 1 and a V_L domain with amino acid SEQ ID NO: 2.

30 In one embodiment the lyophilized formulation or the aqueous pharmaceutical composition of the invention comprises an anti-BAFFR antibody comprising a heavy chain region of SEQ ID NO: 9 and a light chain region of SEQ ID NO: 10.

In one embodiment the lyophilized formulation or the aqueous pharmaceutical composition of the invention comprises the anti-BAFFR antibody MOR6654 or MOR6654B.

5 The invention also comprises a delivery device including the aqueous pharmaceutical composition of the invention.

The invention also comprises a pre-filled syringe including the aqueous pharmaceutical composition of the invention.

10 The invention also comprises a method for delivering an anti-BAFFR antibody to a mammal, comprising a step of administering to the patient an aqueous pharmaceutical composition of the invention.

The invention also comprises a lyophilized formulation or an aqueous pharmaceutical composition according to the invention for use in treating a disease or disorder that is mediated by BAFF receptor or that can be treated by killing or depleting B cells.

15 The invention also comprises a lyophilized formulation or aqueous pharmaceutical composition according to the invention for use in the treatment of autoimmune diseases.

The invention also comprises a lyophilized formulation or aqueous pharmaceutical composition according to the invention for use in the treatment of B cell neoplasms, such as lymphoma, leukemia or myeloma.

20 The invention also provides a lyophilized formulation or aqueous pharmaceutical composition according to the invention for use in the treatment of rheumatoid arthritis, systemic lupus erythematosus, or Pemphigus vulgaris.

Aqueous pharmaceutical compositions with high concentration of anti-BAFFR antibodies

25 The invention relies, at least partly, in the formulation properties of antibodies such as MOR6654 and MOR6654B, which retain remarkable stability and bioactive properties when formulated in a high concentration either as a liquid (aqueous) or lyophilisate composition.

30 As used herein, an "aqueous" pharmaceutical composition is a composition suitable for pharmaceutical use, wherein the aqueous carrier is distilled water. A composition suitable for pharmaceutical use may be sterile, homogeneous and/or isotonic. Aqueous pharmaceutical compositions may be prepared either directly in an aqueous form, for example in pre-filled syringe ready for use (the "liquid formulations") or as lyophilisate to be reconstituted shortly before use. As used herein, the term "aqueous pharmaceutical
35 composition" refers to the liquid formulation or reconstituted lyophilized formulation. In

certain embodiments, the aqueous pharmaceutical compositions of the invention are suitable for parenteral administration to a human subject. In a specific embodiment, the aqueous pharmaceutical compositions of the invention are suitable for subcutaneous administration.

5 As used herein, the phrase "parenteral administration" means mode of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection
10 and infusion.

The use of antibodies as the active ingredient of pharmaceuticals is now widespread, including the products HERCEPTIN™ (trastuzumab), RITUXAN™ (rituximab), SYNAGIS™ (palivizumab), etc. Techniques for purification of therapeutic antibodies to a pharmaceutical grade are well known in the art.

15 The composition will usually be non-pyrogenic e.g. containing <1 EU (endotoxin unit, a standard measure) per dose, and preferably <0.1 EU per dose. The composition is preferably gluten-free.

In specific embodiments, the aqueous pharmaceutical compositions of the invention exhibit low to undetectable levels of antibody aggregation or degradation, with very little
20 to no loss of the biological activities during manufacture, preparation, transportation and long periods of storage, the concentration of the anti-BAFFR antibody being at least about 50mg/ml, 100mg/ml, 150mg/ml, 200mg/ml, 250mg/ml, or 300mg/ml.

In one aspect, the invention relates to an aqueous pharmaceutical composition with high concentration of anti-BAFFR antibodies.

25 It is known in the art that such high concentration aqueous pharmaceutical compositions can be diluted prior to injection, for example, if lower antibody concentrations are required for specific therapeutic interventions or when treating patients of lower body weight including children. Suitable concentrations can be 25mg/ml or 10mg/ml. Alternatively, the original formulation may be produced with such a lower concentration.

30 The term "antibody" as referred to herein includes whole antibodies and any antigen binding fragment (i. e., "antigen-binding portion") or single chains thereof. A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant
35 region. The heavy chain constant region is comprised of three or four domains, depending on the isotype, C_H1, C_H2, C_H3 and C_H4. Each light chain is comprised of a

light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, C_L . The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of 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. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

The term "antigen-binding portion" of an antibody (or simply "antigen portion"), as used herein, refers to full length or one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., a portion of BAFFR). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include a Fab fragment, a monovalent fragment consisting of the V_L , V_H , C_L and C_H1 domains; a $F(ab)_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the V_H and C_H1 domains; a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989 Nature 341:544-546), which consists of a V_H domain; and an isolated complementarity determining region (CDR).

Furthermore, although the two domains of the Fv fragment, V_L and V_H , are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al., 1988 Science 242:423-426; and Huston et al., 1988 Proc. Natl. Acad. Sci. 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding region" of an antibody. These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

An "isolated antibody", as used herein, refers to an antibody that is substantially free of other antibodies having different antigenic specificities, e.g., an isolated antibody that specifically binds human BAFFR is substantially free of antibodies that specifically bind antigens other than BAFFR. An isolated antibody that specifically binds BAFFR may, however, have cross-reactivity to other antigens, such as BAFFR molecules from other species. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

- 5 The term "human antibody", as used herein, includes antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, e.g., human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework
10 sequences derived from human framework sequences analysis, for example, as described in Knappik, et al. (2000. J Mol Biol 296, 57-86).

The structures and locations of immunoglobulin variable domains, e.g., CDRs, may be defined using well known numbering schemes, e.g., the Kabat numbering scheme, the Chothia numbering scheme, a combination of Kabat and Chothia (AbM), etc. (see, e.g.,
15 Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services (1991), eds. Kabat et al.; Al Lazikani et al. (1997) J. Mol. Bio. 273:927-948). Throughout this specification, the complementarity determining region ("CDR") is defined according to the Kabat definition with the exception of CDRH1 which is the stretch of amino acids defined by a combination of both Kabat and Chothia definitions for this CDR.

- 20 The human antibodies of the invention may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto
25 human framework sequences.

The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human sequences.

- The term "recombinant human antibody", as used herein, includes all human antibodies
30 that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, antibodies isolated from a recombinant, combinatorial human
35 antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences. Such recombinant human antibodies have variable

regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo.

As used herein, "isotype" refers to the antibody class (e.g., IgM, IgA, IgD, IgE and IgG such as IgG1, IgG2, IgG3 or IgG4) that is provided by the heavy chain constant region genes.

The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

As used herein, an antibody that "specifically binds to BAFFR polypeptide" or an "anti-BAFFR antibody" refers to an antibody that binds to human BAFFR polypeptide of SEQ ID NO: 13 with a K_D of 100nM or less, 10nM or less, 1nM or less. An antibody that "cross-reacts with an antigen other than BAFFR" refers to an antibody that binds that antigen with a K_D of 0.5 x 10⁻⁸ M or less, 5 x 10⁻⁹ M or less, or 2 x 10⁻⁹ M or less. An antibody that "does not cross-react with a particular antigen" is intended to refer to an antibody that binds to that antigen, with a K_D of 1.5 x 10⁻⁸ M or greater, or a K_D of 5-10 x 10⁻⁸ M or 1 x 10⁻⁷ M or greater. In certain embodiments, such antibodies that do not cross-react with the antigen exhibit essentially undetectable binding against these proteins in standard binding assays.

In one embodiment, a high concentration of an anti-BAFFR antibody in the aqueous pharmaceutical composition of the invention is at least 50mg/ml. In one embodiment, a high concentration is at least 100mg/ml. In one embodiment, a high concentration is at least 150mg/ml. In one embodiment, a high concentration is at least 200mg/ml. In one embodiment, a high concentration is at least 250mg/ml. In one embodiment, a high concentration is at least 300mg/ml.

In one embodiment, the aqueous pharmaceutical composition of the invention comprises between 50mg/ml and 300mg/ml of an anti-BAFFR antibody, for example, MOR6654, especially MOR6654B.

In one embodiment, the aqueous pharmaceutical composition of the invention comprises between 75mg/ml and 250mg/ml of an anti-BAFFR antibody, for example, MOR6654, especially MOR6654B.

In one embodiment, the aqueous pharmaceutical composition of the invention comprises between 100mg/ml and 250mg/ml of an anti-BAFFR antibody, for example, MOR6654, especially MOR6654B.

5 In one embodiment, the aqueous pharmaceutical composition of the invention comprises between 100mg/ml and 200mg/ml of an anti-BAFFR antibody, for example, MOR6654, especially MOR6654B.

In one embodiment, the aqueous pharmaceutical composition of the invention comprises 150mg/ml of an anti-BAFFR antibody, for example, MOR6654, especially MOR6654B.

10 In one embodiment, the aqueous pharmaceutical composition of the invention comprises about 50mg/ml, about 60mg/ml, about 70mg/ml, about 80mg/ml, about 90mg/ml, about 100mg/ml, about 110mg/ml, about 120mg/ml, about 130mg/ml, about 140mg/ml, about 150mg/ml, about 160mg/ml, about 170mg/ml, about 180mg/ml, about 190mg/ml, about 200mg/ml, about 210mg/ml, about 220mg/ml, about 230mg/ml, about 240mg/ml, about 250mg/ml or about 300mg/ml of an anti-BAFFR antibody, for example, MOR6654,
15 especially MOR6654B.

Furthermore, the aqueous pharmaceutical compositions are stable such that, even after storage for 4 weeks at 2-8°C, less than 5%, 4%, 3%, 2%, 1%, 0.05% or 0.01% of the total anti-BAFFR antibody is aggregated as measured by SEC-HPLC.

20 The aqueous pharmaceutical compositions may include, in addition to the anti-BAFFR antibody, further components such as one or more of the following: (i) a stabilizer; (ii) a buffering agent; (iii) a surfactant; and (iv) a free amino acid. Inclusion of each of such additional components can give compositions with low aggregation of the anti-BAFFR antibody.

25 Suitable stabilizer for use with the invention can act, e.g., as viscosity enhancing agents, bulking agents, solubilizing agents, and/or the like. The stabilizer can be ionic or non ionic (e.g. sugars). As sugars they include, but are not limited to, monosaccharides, e.g., fructose, maltose, galactose, glucose, D-mannose, sorbose and the like; disaccharides, e.g. lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, e.g. raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as
30 mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol) and the like. For example, the sugar may be sucrose, trehalose, raffinose, maltose, sorbitol or mannitol. The sugar may be a sugar alcohol or an amino sugar. Sucrose is particularly useful. As ionic stabilizer they include salts such as NaCl or amino acid components such as arginine-HCl.

35 Suitable buffering agents for use with the invention include, but are not limited to, organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid or phtalic acid; Tris, thomethamine hydrochloride, or

phosphate buffer. In addition, amino acid components can also be used as buffering agent. Such amino acid component includes without limitation glycine and histidine. A histidine buffer is particularly useful.

5 The aqueous pharmaceutical compositions include such buffering agent or pH adjusting agent to provide improved pH control. In one embodiment, an aqueous pharmaceutical composition of the invention has a pH between 5.0 and 8.0, between 5.0 and 7.0, between 6.0 and 8.0, or between 6.0 and 7.0. In a specific embodiment, an aqueous pharmaceutical composition of the invention has a pH of about 6.5.

10 As used herein, the term "surfactant" herein refers to organic substances having amphipathic structures; i.e., they are composed of groups of opposing solubility tendencies, typically an oil-soluble hydrocarbon chain and a water-soluble ionic group. Surfactants can be classified, depending on the charge of the surface-active moiety, into anionic, cationic and dispersing agents for various pharmaceutical compositions and preparations of biological materials.

15 Suitable surfactants for use with the invention include, but are not limited to, non-ionic surfactants, ionic surfactants and zwitterionic surfactants. Typical surfactants for use with the invention include, but are not limited to, sorbitan fatty acid esters (e.g. sorbitan monocaprylate, sorbitan monolaurate, sorbitan monopalmitate), sorbitan trioleate, glycerine fatty acid esters (e.g. glycerine monocaprylate, glycerine monomyristate, 20 glycerine monostearate), polyglycerine fatty acid esters (e.g. decaglyceryl monostearate, decaglyceryl distearate, decaglyceryl monolinoleate), polyoxyethylene sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan trioleate, polyoxyethylene sorbitan tristearate), 25 polyoxyethylene sorbitol fatty acid esters (e.g. polyoxyethylene sorbitol tetrastearate, polyoxyethylene sorbitol tetraoleate), polyoxyethylene glycerine fatty acid esters (e.g. polyoxyethylene glyceryl monostearate), polyethylene glycol fatty acid esters (e.g. polyethylene glycol distearate), polyoxyethylene alkyl ethers (e.g. polyoxyethylene lauryl ether), polyoxyethylene polyoxypropylene alkyl ethers (e.g. polyoxyethylene 30 polyoxypropylene glycol, polyoxyethylene polyoxypropylene propyl ether, polyoxyethylene polyoxypropylene cetyl ether), polyoxyethylene alkylphenyl ethers (e.g. polyoxyethylene nonylphenyl ether), polyoxyethylene hydrogenated castor oils (e.g. polyoxyethylene castor oil, polyoxyethylene hydrogenated castor oil), polyoxyethylene beeswax derivatives (e.g. polyoxyethylene sorbitol beeswax), polyoxyethylene lanolin derivatives (e.g. polyoxyethylene lanolin), and polyoxyethylene fatty acid amides (e.g. 35 polyoxyethylene stearic acid amide); C₁₀-C₁₈ alkyl sulfates (e.g. sodium cetyl sulfate, sodium lauryl sulfate, sodium oleyl sulfate), polyoxyethylene C₁₀-C₁₈ alkyl ether sulfate with an average of 2 to 4 moles of ethylene oxide units added (e.g. sodium

polyoxyethylene lauryl sulfate), and C₁-C₁₈ alkyl sulfosuccinate ester salts (e.g. sodium lauryl sulfosuccinate ester); and natural surfactants such as lecithin, glycerophospholipid, sphingophospholipids (e.g. sphingomyelin), and sucrose esters of C₁₂-C₁₈ fatty acids. A composition may include one or more of these surfactants. Preferred surfactants are polyoxyethylene sorbitan fatty acid esters e.g. polysorbate 20, 40, 60 or 80. Polysorbate 80 (Tween 80) is particularly useful.

Suitable free amino acids for use with the invention include, but are not limited to, arginine, lysine, histidine, ornithine, isoleucine, leucine, alanine, glycine glutamic acid or aspartic acid. The inclusion of a basic amino acid is preferred *i.e.* arginine, lysine and/or histidine. If a composition includes histidine then this may act both as a buffering agent and a free amino acid, but when a histidine buffer is used it is typical to include a non-histidine free amino acid e.g. to include histidine buffer and lysine. An amino acid may be present in its D- and/or L- form, but the L-form is typical. The amino acid may be present as any suitable salt e.g. a hydrochloride salt, such as arginine-HCl.

When present, components (i) to (iv) will be at a concentration sufficient to maintain the anti-BAFFR antibody in a form which is active and soluble after either

(i) lyophilisation and storage and reconstitution (for lyophilisates), or

(ii) conditioning in dosing units and storage (for liquid formulations).

Thus a sugar may be present in the aqueous pharmaceutical composition of the invention, e.g. after reconstitution of a lyophilisate in water, at a concentration of between 3 and 400mM e.g. 50-300mM, 200-300mM, 250-300mM. A concentration of 270 mM sucrose is useful.

A buffering agent may be present in the aqueous pharmaceutical composition of the invention, e.g. after reconstitution of a lyophilisate in water, at a concentration of between 1 and 60 mM e.g. 10-40 mM, 15-30 mM, 15-25 mM. A concentration of 21 mM histidine buffer is useful.

A surfactant may be present in the aqueous pharmaceutical composition of the invention, e.g. after reconstitution of a lyophilisate in water, at a concentration of up to 0.2% (by volume) e.g. 0.01-0.1%, 0.03-0.08%, 0.04-0.08%. A concentration of 0.06% polysorbate 80 or polysorbate 20 is useful.

A free amino acid may be present in the aqueous pharmaceutical composition of the invention, e.g. after reconstitution of a lyophilisate in water, at a concentration of between 2 and 100 mM e.g. 10-80 mM, 20-70 mM, 30-60 mM, 40-60 mM. A concentration of 51mM arginine-HCl or 60 mM glycine-HCl is useful.

A formulation containing histidine buffer, sucrose and polysorbate 80 has been shown to be suitable for lyophilisation of antibody MOR6654B at a concentration of at least 150mg/ml after reconstitution.

5 In one embodiment the aqueous pharmaceutical composition consists of 150 mg/ml MOR6654 or MOR6654B, 21 mM histidine, 270 mM sucrose and 0.06% polysorbate 80.

In one embodiment the aqueous pharmaceutical composition consists of 150 mg/ml MOR6654 or MOR6654B, 21 mM histidine, 270 mM sucrose, 0.06% polysorbate 80 and 60 mM glycine-HCl.

10 In one embodiment the aqueous pharmaceutical composition consists of 150 mg/ml MOR6654 or MOR6654B, 21 mM histidine, 270 mM sucrose, 0.06% polysorbate 80 and 51 mM arginine-HCl.

In one embodiment the aqueous pharmaceutical composition consists of 200 mg/ml MOR6654 or MOR6654B, 21 mM histidine, 270 mM sucrose, 0.06% polysorbate 80 and 51 mM arginine-HCl.

15 In one embodiment the aqueous pharmaceutical composition consists of 75 mg/ml MOR6654 or MOR6654B, 21 mM histidine, 270 mM sucrose, 0.06% polysorbate 80 and 51 mM arginine-HCl.

20 Other contemplated excipients, which may be utilized in the aqueous pharmaceutical compositions of the invention include, for example, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, lipids such as phospholipids or fatty acids, steroids such as cholesterol, protein excipients such as serum albumin (human serum albumin), recombinant human albumin, gelatin, casein, salt-forming counterions such sodium and the like. These and additional known pharmaceutical excipients and/or additives suitable for use in the formulations of the invention are known in the art, e.g., as listed in "The Handbook of Pharmaceutical Excipients, 4th edition, Rowe et al., Eds., American Pharmaceuticals Association (2003); and Remington: the Science and Practice of Pharmacy, 21th edition, Gennaro, Ed., Lippincott Williams & Wilkins (2005).

30 The aqueous pharmaceutical compositions of the invention may include further active ingredients in addition to the anti-BAFFR antibody. Further pharmacological agents may include, for instance, chemotherapeutic compounds.

Lyophilisates

35 Techniques for lyophilisation of antibodies are well known in the art e.g. see John F. Carpenter and Michael J. Pikal, 1997 (*Pharm. Res.* 14, 969-975); Xialin (Charlie) Tang and Michael J. Pikal, 2004 (*Pharm. Res.* 21, 191-200). For example, the monoclonal antibody products SYNAGIS™, REMICADE™, RAPTIVA™, SIMULECT™, XOLAIR™

and HERCEPTIN™ are supplied as lyophilisates. These antibodies are reconstituted to various final concentrations e.g. SIMULECT™ is reconstituted to a concentration of 4 mg/ml antibody, REMICADE™ is reconstituted to a concentration of 10 mg/ml, HERCEPTIN™ to 21 mg/ml, SYNAGIS™ and RAPTIVA™ to 100 mg/ml, and XOLAIR™ to 125 mg/ml.

Pre-lyophilisates, lyophilisates and aqueous reconstitution

Before a lyophilisate can be administered to a patient it should be reconstituted with an aqueous reconstituent. This step permits antibody and other components in the lyophilisate to re-dissolve to give a solution which is suitable for injection to a patient.

- 10 The volume of aqueous material used for reconstitution dictates the concentration of the antibody in a resulting pharmaceutical composition. Reconstitution with a smaller volume of reconstituent than the pre-lyophilisation volume provides a composition which is more concentrated than before lyophilisation. The reconstitution factor (volume of formulation after lyophilization:volume of formulation before lyophilization) may be from 1:0.5 to 1:6.
- 15 A reconstitution factor of 1:3 is useful. As mentioned above, lyophilisates of the invention can be reconstituted to give aqueous compositions with an anti-BAFFR antibody concentration of at least 50 mg/ml, 100 mg/ml, 150 mg/ml, 200 mg/ml, 250 mg/ml or 300 mg/ml, and the volume of reconstituent will be selected accordingly. If required, the reconstituted formulation can be diluted prior to administration to a patient as appropriate
- 20 to deliver the intended dose.

Typical reconstituents for lyophilized antibodies include sterile water or buffer, optionally containing a preservative. If the lyophilisate includes a buffering agent then the reconstituent may include further buffering agent (which may be the same as or different from the lyophilisate's buffering agent) or it may instead include no buffering agent (e.g. WFI (water for injection), or physiological saline).

25 When present, components (i) to (iv) will be at a pre-lyophilisation concentration sufficient to maintain the anti-BAFFR antibody in a form which is active and soluble after storage (under normal conditions) and reconstitution. The components will also be present after reconstitution.

30 Thus a sugar, such as sucrose or trehalose, may be present before lyophilisation at a concentration of between 3 and 300 mM e.g. 15-200 mM, 30-150 mM, 80-100 mM. A concentration of 90 mM sucrose is useful. A buffering agent, such as histidine, may be present before lyophilisation at a concentration of between 1 and 60 mM e.g. 3-30 mM, 5-20 mM, 5-15 mM. A concentration of 7 mM histidine buffer is useful. A surfactant, such

35 as polysorbate 80 or polysorbate 20 may be present before lyophilisation at a concentration of up to 0.2% (by volume) e.g. 0.01-0.1%, 0.01-0.08%, 0.01-0.04%. A concentration of 0.02% polysorbate 80 or polysorbate 20 is useful. A free amino acid,

such as arginine or glycine, may be present before lyophilisation at a concentration of between 2 and 80 mM e.g. 3-50 mM, 6-30 mM, 10-25 mM, 15-20 mM. A concentration of 17 mM arginine-HCl or 20 mM glycine-HCl is useful. The anti-BAFFR antibody is present before lyophilization at a concentration of between 20mg/ml and 120mg/ml, e.g. 20mg/ml, 30 mg/ml, 40mg/ml, 50mg/ml, 60mg/ml, 66.6mg/ml, 70mg/ml, 80mg/ml, 90mg/ml, 100mg/ml, 110mg/ml, or 120mg/ml. A concentration of 50 mg/ml is useful.

The pre-lyophilisate of the invention has a pH between 5.0 and 8.0, between 5.0 and 7.0, between 6.0 and 8.0, or between 6.0 and 7.0. In a specific embodiment, the pre-lyophilisate of the invention has a pH of about 6.5.

10 In one embodiment the pre-lyophilisate of the invention has a molar ratio of sucrose:antibody of 270:1 and a molar ratio of histidine:antibody of 21:1.

In one embodiment the pre-lyophilisate of the invention has a molar ratio of sucrose:antibody of 270:1, a molar ratio of histidine:antibody of 21:1, and a molar ratio of arginine-HCl:antibody of 51:1.

15 In one embodiment the pre-lyophilisate of the invention has a molar ratio of sucrose:antibody of 270:1, a molar ratio of histidine:antibody of 21:1, and a molar ratio of glycine-HCl:antibody of 60:1.

In one embodiment the pre-lyophilisate of the invention has a molar ratio of sucrose:antibody of 203:1, a molar ratio of histidine:antibody of 16:1, and a molar ratio of arginine-HCl:antibody of 38:1.

A formulation containing histidine buffer, sucrose, polysorbate 80 and, optionally arginine or glycine has been shown to be suitable for lyophilisation of antibody MOR6654B. After reconstitution, the components of the lyophilisate may be present at a concentration of the aqueous pharmaceutical compositions as described hereinbefore.

25 ***Target diseases and disorders***

The aqueous pharmaceutical compositions of the invention comprising anti-BAFFR antibodies can be used to treat, ameliorate or prevent a variety of diseases or disorders. Pharmaceutical compositions comprising anti-BAFFR antibodies are particularly useful to treat BAFFR related disorders such as autoimmune disorders, e.g., systemic lupus erythematosus, Pemphigus vulgaris, rheumatoid arthritis, multiple sclerosis and B cell neoplasms such as acute lymphoblastic leukemia (ALL) and B-cell chronic lymphocytic leukemia (CLL).

As used herein, "a BAFFR-related disorder" includes conditions associated with or characterized by aberrant BLYS levels and/or diseases or conditions that can be treated by depleting or killing B cells. These includes, without limitations, inflammatory

conditions, autoimmune diseases, severe infections, and organ or tissue transplant rejection. These further include B-cell neoplasms.

For example, the aqueous pharmaceutical compositions of the invention comprising anti-BAFFR antibodies may be used for the treatment, amelioration or prevention of recipients of heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants, including allograft rejection or xenograft rejection, and for the prevention of graft-versus-host disease, such as following bone marrow transplant, and organ transplant associated arteriosclerosis. Further, the aqueous pharmaceutical compositions of the invention are useful in solid organ transplantation and in antibody-mediated acute and chronic transplant rejection.

The aqueous pharmaceutical compositions of the invention comprising anti-BAFFR antibodies are useful for the treatment, prevention, or amelioration of autoimmune disease and of inflammatory conditions, in particular inflammatory conditions with an etiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, including inflammatory conditions and rheumatic diseases involving bone loss, inflammatory pain, spondyloarthropathies including ankylosing spondylitis, Reiter syndrome, reactive arthritis, psoriatic arthritis, and enteropathic arthritis, hypersensitivity (including both airways hypersensitivity and dermal hypersensitivity) and allergies. Specific auto-immune diseases for which antibodies of the invention may be employed include autoimmune haematological disorders (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), acquired hemophilia A, cold agglutinin disease, cryoglobulinemia, thrombotic thrombocytopenic purpura, Sjögren's syndrome, systemic lupus erythematosus, inflammatory muscle disorders, polyarthritides, scleroderma, vasculitis such as cryoglobulinemia, large vessel vasculitides such as giant cell arteritis, polymyalgia rheumatica, necrotizing vasculitides, including anti-neutrophil cytoplasmic antibody-associated vasculitis, Takayasu's arteritis, polyarteritis nodosa, Henoch-Schonlein purpura, and Churg-Strauss syndrome, IgM mediated neuropathy, seronegative spondylarthritis, opsoclonus myoclonus syndrome, Wegener granulomatosis, dermatomyositis, anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, pemphigus vulgaris, pemphigus foliaceus, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis, Crohn's disease and Irritable Bowel Syndrome), endocrine ophthalmopathy, Graves' disease, sarcoidosis, multiple sclerosis, neuromyelitis optica, primary biliary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior, intermediate and posterior as well as panuveitis), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and

glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy), acute nephritic lupus, tumors, inflammatory disease of skin and cornea, myositis, loosening of bone implants, metabolic disorders, such as atherosclerosis, diabetes, and dislipidemia.

- 5 The aqueous pharmaceutical compositions of the invention may also be useful in preventing, ameliorating or treating B-cell neoplasms. Examples of such diseases and conditions include, but are not limited to, B-cell Non-Hodgkin's lymphomas, such as small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, mantle cell lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, diffuse large cell
10 lymphoma, and Burkitt's lymphoma; acute lymphoblastic leukemia (ALL), precursor B-lymphoblastic leukemia; B-cell chronic lymphocytic leukemia (CLL), and multiple myeloma. Other B-cell neoplasms are encompassed within the scope of the invention.

Patient administration

- A pharmaceutical composition of the invention can be administered to a patient.
15 Administration will typically be via a syringe. Thus the invention provides a delivery device (e.g. a syringe) including a pharmaceutical composition of the invention (e.g., pre-filled syringe). Patients will receive an effective amount of the anti-BAFFR antibody as the principal active ingredient *i.e.* an amount that is sufficient to treat, ameliorate, or prevent the disease or disorder in question. Therapeutic effects may also include
20 reduction in physical symptoms. The optimum effective amount and concentration of antibody for any particular subject will depend upon various factors, including the patient's age size health and/or gender, the nature and extent of the condition, the activity of the particular antibody, the rate of its clearance by the body, and also on any possible further therapeutic(s) administered in combination with the antibody. The
25 effective amount delivered for a given situation can be determined within the judgment of a clinician. For purposes of the present invention, an effective dose may be from about 0.005 mg/kg to about 50 mg/kg, or about 0.05 mg/kg to about 10 mg/kg. Known antibody-based pharmaceuticals provide guidance in this respect *e.g.* HERCEPTIN™ is administered with an initial loading dose of 4 mg/kg body weight and a weekly
30 maintenance dose of 2 mg/kg body weight; RITUXAN™ is administered weekly at 375 mg/m²; SYNAGIS™ is administered intramuscularly at 15 mg/kg body weight; *etc.*

The invention provides a method for delivering a monoclonal antibody to a mammal, comprising a step of administering to the patient a pharmaceutical composition of the invention.

- 35 The invention also provides a method for delivering a monoclonal antibody to a mammal, comprising steps of: (i) reconstituting a lyophilisate of the invention to give an aqueous formulation, and (ii) administering the aqueous formulation to the patient. Step (ii) ideally

takes place within 24 hours of step (i) e.g. within 12 hours, within 6 hours, within 3 hours, or within 1 hour.

The invention also provides formulations of the invention for use as medicaments e.g. for use in delivering an antibody to a mammal, or for use in treating, preventing or ameliorating one or more of the diseases and disorders described above.

The mammal is preferably a human but may also be, for example, a horse or a cow or a dog or a cat. The antibodies will ideally be chosen to match the target species e.g. a human antibody for human administration, an equine antibody for horses, a canine antibody for dogs, etc. If native host antibodies are not available then transfer of antibody specificity from one species to another can be achieved by transfer of CDR residues (and typically, in addition, one or more framework residues) from a donor antibody into a recipient framework from the host species e.g. as in humanization. Equinized, bovinized, caninized and felinized antibodies are known in the art. The antibody will bind to BAFFR from the target species, but it may also cross-react with BAFFR from other species.

Dosage can be by a single dose schedule or a multiple dose schedule.

Ingredients for forming compositions of the invention (e.g. lyophilisates and reconstituents) may be supplied in hermetically-sealed containers.

The anti-BAFFR antibody

The invention concerns the formulation of anti-BAFFR antibodies and more specifically MOR6654 and MOR6654B.

One suitable antibody that can be comprised in the pharmaceutical compositions of the invention is the human recombinant antibody MOR6654, structurally characterized as further described below. The V_H amino acid sequence of such isolated anti-BAFFR antibody is shown in SEQ ID NO: 1. The V_L amino acid sequence of such isolated anti-BAFFR antibody is shown in SEQ ID NO: 2. An example of the full length heavy chain amino acid sequence of such isolated anti-BAFFR antibody is shown in SEQ ID NO: 9. An example of the full-length light chain amino acid sequence of such isolated anti-BAFFR antibody is shown in SEQ ID NO: 10. Another example of heavy and light chain amino acid sequences of such isolated anti-BAFFR antibodies are those encoded by the nucleotide sequences of SEQ ID NO: 11 and SEQ ID NO: 12 respectively. Another example of heavy and light chain amino acid sequences of antibodies are those encoded by corresponding DNA sequences contained in plasmid pBW510 as deposited by Novartis Pharma AG, Forum 1, CH-4002 Basel, Switzerland, at DSMZ on April 29, 2009 with accession number DSM22542.

Other anti-BAFFR antibodies that can be used for preparing the pharmaceutical compositions of the invention include anti-BAFFR antibodies, with amino acids that have

been mutated by amino acid deletion, insertion or substitution, yet have no more than 1, 2, 3, 4 or 5 amino acid deletion, insertion or substitution in either the heavy or light chain regions described above. In a specific embodiment, such amino acid changes appear only within the framework and/or constant regions and the CDR regions are 100% identical to the heavy chain CDR1, CDR2 and CDR3 regions of SEQ ID NO: 3, 4 and 5 and to the light chain CDR1, CDR2 and CDR3 regions of SEQ ID NO: 6, 7, and 8 respectively. In one more specific embodiment, the changes that have been made are only conservative amino acid substitutions outside of the CDR regions.

Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues outside of the CDR regions of an anti-BAFFR antibody, can be replaced with other amino acid residues from the same side chain family, and the altered antibody can be tested for retained function, in particular the same binding properties to BAFFR.

Antibodies may typically be glycosylated. N-linked glycans attached to the C_H2 domain of a heavy chain, for instance, can influence C1q and FcR binding, and aglycosylated antibodies may have lower or different affinity for these receptors. The glycan structure can also affect activity *e.g.* differences in complement-mediated cell death may be seen depending on the number of galactose sugars (0, 1 or 2) at the terminus of a glycan's biantennary chain. An antibody's glycans preferably do not lead to a human immunogenic response after administration.

Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated or non-fucosylated antibody having reduced amounts of or no fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the antibody-dependent cell-mediated cytotoxicity (ADCC) ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with an altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang et al. describes a cell line with a functionally disrupted *FUT8* gene, which encodes a fucosyl transferase, such that

antibodies expressed in such a cell line exhibit hypofucosylation or are devoid of fucosyl residues. Therefore, in one embodiment, the anti-BAFFR antibodies that are included in the pharmaceutical compositions of the invention are produced by recombinant expression in a cell line which exhibit hypofucosylation or non-fucosylation pattern, for example, a mammalian cell line with deficient expression of the *FUT8* gene encoding fucosyltransferase.

As used herein, the term MOR6654 encompasses any type of glycosylation pattern. In a specific embodiment, the pharmaceutical compositions comprises an anti-BAFFR antibody consisting of MOR6654 as produced in a cell line which exhibits a hypofucosylation or non-fucosylation pattern, such as MOR6654B, which exhibit non-fucosylation pattern (devoid of fucosyl residues). PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R.L. et al., 2002 J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana et al., 1999 Nat. Biotech. 17:176-180). Eureka Therapeutics further describes genetically engineered CHO mammalian cells capable of producing antibodies with altered mammalian glycosylation pattern devoid of fucosyl residues (http://www.eurekainc.com/about_us/companyoverview.html). Alternatively, the anti-BAFFR antibodies can be produced in yeasts or filamentous fungi engineered for mammalian-like glycosylation pattern and capable of producing antibodies lacking fucose as glycosylation pattern (see for example EP1297172B1).

Another modification of the anti-BAFFR antibodies herein that is contemplated by the invention is pegylation. An antibody can be pegylated to, for example, increase the biological (e.g., serum) half-life of the antibody. To pegylate an antibody, the antibody, or fragment thereof, typically may be reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. The pegylation can be carried out by an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer).

As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Methods for pegylating

proteins are known in the art and can be applied to the antibodies of the invention. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

Any other natural or non-natural post-translational modification of anti-BAFFR antibodies (e.g. MOR6654) is further contemplated as specific embodiments of anti-BAFFR antibodies that could be used for preparing the pharmaceutical compositions of the invention.

Antibodies can be prepared in a form free from products with which they would naturally be associated. Contaminant components of an antibody's natural environment include materials such as enzymes, hormones, or other host cell proteins.

10 EXAMPLES

Preparing anti-BAFFR antibodies

Antibody MOR6654 binds specifically to BAFFR and is also described in reference WO2010/007082. It is a human IgG1 kappa antibody obtained via phage display. Its heavy and light chains consist of SEQ ID NOs: 9 and 10. The Tables 1 and 2 below summarize the sequence characteristics of MOR6654.

This antibody may be produced in mammalian host cells, such as, a CHO cell line transfected with expression vectors carrying heavy and light chain coding sequences under suitable expression promoters.

This antibody is preferably produced in a mammalian cell line, e.g. a CHO cell line, wherein the gene encoding fucosyltransferase (FUT8 gene) has been inactivated. The resulting antibody is non-fucosylated and designated here as MOR6654B.

Table 1: Brief description of the sequences listed in the sequence listing of Table 2

SEQ ID NO:	Description of the sequence
1	Amino acid sequence of the variable region (V _H) of the heavy chain of MOR6654
2	Amino acid sequence of the variable region (V _L) of the light chain of MOR6654
3	Amino acid sequence of HCDR1 of MOR6654
4	Amino acid sequence of HCDR2 of MOR6654
5	Amino acid sequence of HCDR3 of MOR6654
6	Amino acid sequence of LCDR1 of MOR6654
7	Amino acid sequence of LCDR2 of MOR6654
8	Amino acid sequence of LCDR3 of MOR6654

9	Amino acid sequence of the full length heavy chain of MOR6654
10	Amino acid sequence of the full length light chain of MOR6654
11	Nucleotide sequence encoding SEQ ID NO:1
12	Nucleotide sequence encoding SEQ ID NO:2
13	Human BAFFR amino acid sequence
14	Full length nucleotide sequence (including leader sequence and constant part) of MOR6654 heavy chain; nt 1-57 = leader; nt 58-429 = VH; nt 430-1419 = constant region (hlgG1)
15	Full length nucleotide sequence (including leader sequence and constant part) of MOR6654 light chain; nt 1-60 = leader; nt 61-384 = VL; nt 385-705 = constant region (hkappa)

Table 2: Sequence listing

SEQ ID NO:	Amino acid or Nucleotide Sequence
1	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWIRQSPGRGLEWL GRIYYRSKWYNSYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARY DWVPKIGVFDSWGQGTLTVSS
2	DIVLTQSPATLSLSPGERATLSCRASQFISSSYLSWYQQKPGQAPRLLIYGSS SRATGVPARFSGSGSGTDFTLTISSELPEDFAVYYCQQLYSSPMTFGQGTKV EIK
3	GDSVSSNSAAWG
4	RIYYRSKWYNSYAVSVKS
5	YDWVPKIGVFDS
6	RASQFISSSYLS
7	GSSSRAT
8	QQLYSSPMT
9	QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSAAWGWIRQSPGRGLEWLG RIYYRSKWYNSYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARYD WVPKIGVFDSWGQGTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPPSSSLGTQTYIC NVNHKPSNTKVKDRVEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV SVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYS KLTVDKSRWQQGNVDFSCSVMHEALHNHYTQKSLSLSPGK
10	DIVLTQSPATLSLSPGERATLSCRASQFISSSYLSWYQQKPGQAPRLLIYGSS SRATGVPARFSGSGSGTDFTLTISSELPEDFAVYYCQQLYSSPMTFGQGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS

	FNRGEC
11	<p>CAGGTGCAGCTGCAGCAGAGCGGCCAGGCCTGGTCAAGCCCTCTCAGA CCCTGTCACTGACCTGCGCCATTTTCAGGCGACAGCGTGAGCAGCAACAG CGCCGCTGGGGCTGGATCAGGCAGAGCCCCGGTAGGGGCTGGAATG GCTGGGCAGGATCTACTACAGGTCCAAGTGGTACAACAGCTACGCCGTG AGCGTGAAGAGCAGGATCACCATCAACCCTGACACCAGCAAGAACCAGTT CTCCTGACAGCTCAACAGCGTGACCCCCGAGGACACCCGCGTGTACTAC TGCGCCAGATACGACTGGGTGCCCAAGATCGGCGTGTTCGACAGCTGGG GCCAGGGCACCTGGTGACCGTGTCAAGC</p>
12	<p>GATATCGTGCTGACACAGAGCCCCGCCACCCTGAGCCTGAGCCCAGGCG AGAGGGCCACCCTGTCTGTCAGGGCCAGCCAGTTTATCAGCAGCAGCTA CCTGTCTGGTATCAGCAGAAGCCCCGGCCAGGCCCTAGACTGCTGATC TACGGCAGCTCCTCTCGGGCCACCGGCGTGCCCCGCCAGGTTTCAGCGGC AGCGGCTCCGGCACCGACTTCACCCTGACAATCAGCAGCCTGGAGCCCG AGGACTTCGCCGTGTACTACTGCCAGCAGCTGTACAGCTCACCCATGACC TTCGGCCAGGGCACCAAGGTGGAGATCAAG</p>
13	<p>MRRGPRSLRGRDAPAPTPCVPAECFDLLVRHCVACGLLRTPRKPAGASSP APRTALQPQESVGAGAGEAALPLPGLLFGAPALLGLALVLAALVGLVSWRR RQRRLRGASSAEAPDGDKDAPEPLDKVILSPGISDATAPAWPPPGEDPGTT PPGHSVPVPATELGSTELVTTKTAGPEQQ</p>
14	<p>ATGGCCTGGGTGTGGACCCTGCCCTTCTGATGGCCGCTGCCCAGTCAG TGCAGGCCAGGTGCAGCTGCAGCAGAGCGGCCAGGCCTGGTCAAGC CCTCTCAGACCCTGTCACTGACCTGCGCCATTTTCAGGCGACAGCGTGAG CAGCAACAGCGCCGCTGGGGCTGGATCAGGCAGAGCCCCGGTAGGGG CCTGGAATGGCTGGGCAGGATCTACTACAGGTCCAAGTGGTACAACAGC TACGCCGTGAGCGTGAAGAGCAGGATCACCATCAACCCTGACACCAGCA AGAACCAGTTCTCACTGCAGCTCAACAGCGTGACCCCCGAGGACACCGC CGTGTACTACTGCGCCAGATACGACTGGGTGCCCAAGATCGGCGTGTTC GACAGCTGGGGCCAGGGCACCCCTGGTGACCGTGTCAAGCGCCAGCACC AAGGGCCCCAGCGTGTCCCCCTGGCCCCCAGCAGCAAGAGCACCAGC GCGGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAG CCCGTGACCGTGTCTGGAACAGCGGAGCCCTGACCTCCGGCGTGCACA CCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGT GGTGACAGTGCCCAGCAGCAGCCTGGGCACCCAGACCTACATCTGCAAC GTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAGCCCA AGAGCTGCGACAAGACCCACACCTGCCCCCCCTGCCAGCCCCAGAGCT GCTGGGCGGACCCTCCGTGTTCTGTTCCCCCCCCAAGCCCAAGGACACC CTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTGGACGTGA GCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGA GGTGCACAACGCCAAGACCAAGCCCAGAGAGGAGCAGTACAACAGCACC TACAGGGTGGTGTCCGTGCTGACCGTGTGACACCAGGACTGGCTGAACG GCAAGGAATACAAGTGCAAGGTCTCCAACAAGGCCCTGCCAGCCCCAT CGAAAAGACCATCAGCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGT GTACACCCTGCCCCCCCTCCCGGGAGGAGATGACCAAGAACCAGGTGTCC CTGACCTGTCTGGTGAAGGGCTTCTACCCAGCGACATCGCCGTGGAGT GGGAGAGCAACGGCCAGCCCAGAGAACAATAAGACCACCCCCCAGT GCTGGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGAC AAGTCCAGGTGGCAGCAGGGCAACGTGTTTCAGCTGCAGCGTGATGCAGC AGGCCCTGCACAACCACTACACCCAGAAGAGCCTGAGCCTGTCCCCCGG CAAG</p>
15	<p>ATGAGCGTGCTGACCCAGGTGCTGGCTCTGCTGCTGCTGTGGCTGACCG</p>

<p>GCACCAGATGCGATATCGTGCTGACACAGAGCCCCGCCACCCTGAGCCT GAGCCCAGGGCAGAGGGCCACCCTGTCCTGCAGGGCCAGCCAGTTTATC AGCAGCAGCTACCTGTCCTGGTATCAGCAGAAGCCCGGCCAGGCCCTA GACTGCTGATCTACGGCAGCTCCTCTCGGGCCACCGGCGTGCCCGCCAG GTTCAGCGGCAGCGGCTCCGGCACCGACTTCACCCTGACAATCAGCAGC CTGGAGCCCAGGACTTCGCCGTGTACTACTGCCAGCAGCTGTACAGCT CACCCATGACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGCGTACGGT GGCCGCTCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAG AGCGGCACCGCCAGCGTGGTGTGCCTGCTGAACAACCTTCTACCCCCGGG AGGCCAAGGTGCAGTGGAAAGTGGACAACGCCCTGCAGAGCGGCAACA GCCAGGAGAGCGTCACCGAGCAGGACAGCAAGGACTCCACCTACAGCCT GAGCAGCACCCCTGACCCTGAGCAAGGCCGACTACGAGAAGCATAAGGTG TACGCCTGCGAGGTGACCCACCAGGGCCTGTCCAGCCCCGTGACCAAGA GCTTCAACAGGGGCGAGTGC</p>
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Examples of formulations

A high concentration lyophilized or liquid formulation of MOR6654B was desired and so formulation studies were performed. A lyophilized formulation comprising a sugar, a buffering agent and a surfactant was stable and could maintain high antibody concentrations after reconstitution.

Three formulations (F1, F2, F3) of MOR6654B at 150 mg/vial and one formulation at 200 mg/vial (F3b) were evaluated for stability. Formulations F1, F2 and F3 had, prior to lyophilisation, 50mg/ml MOR6654B at pH 6.5, and formulation F3b 66.6mg/ml at pH 6.5. The four formulations had a fill volume of 3.6 ml and included buffer, sugar, surfactant and free amino acid as follows in Table 3:

Table 3: Examples of formulations

	MOR6654B	Buffer	Sugar	Surfactant	Amino acid
F1	50mg/ml	7mM histidine	90mM sucrose	0.02% polysorbate 80	-
F2	50mg/ml	7mM histidine	90mM sucrose	0.02% polysorbate 80	20mM glycine-HCl
F3	50mg/ml	7mM histidine	90mM sucrose	0.02% polysorbate 80	17mM arginine-HCl
F3b	66.6mg/ml	7mM histidine	90mM sucrose	0.02% polysorbate 80	17mM arginine-HCl

The lyophilisates were reconstituted with WFI (1ml) to give a reconstituted volume of 1.2ml (20% overage; 1/3 the original aqueous volume). The reconstituted compositions were as in Table 4:

5 **Table 4:** Examples of formulations

	MOR6654B	Buffer	Sugar	Surfactant	Amino acid
F1	150 mg/ml	21mM histidine	270mM sucrose	0.06% polysorbate 80	-
F2	150 mg/ml	21mM histidine	270mM sucrose	0.06% polysorbate 80	60mM glycine-HCl
F3	150 mg/ml	21mM histidine	270mM sucrose	0.06% polysorbate 80	51mM arginine-HCl
F3b	200 mg/ml	21mM histidine	270mM sucrose	0.06% polysorbate 80	51mM arginine-HCl

The lyophilisation cycle used is reported in Table 5.

Table 5: The lyophilisation cycle parameters

Step	Operation	Time [hh:mm]	Shelf temp.	Chamber pressure
1	Vial loading	As required	20°C	Ambient
2	5°C cooling	00:30	5°C	Ambient
3	5°C hold	03:00	5°C	Ambient
4	Freeze ramp	01:24	5°C to - 37°C	Ambient
5	Freeze hold	04:00	- 37°C	Ambient
6	Chamber Vacuum	00:10	-37°C	0.2 mbar ^a
7	Primary drying ramp	16:00	-37°C to 25°C	0.2 mbar ^a
8	Secondary drying hold	24:00	25°C	0.2 mbar ^a
11	Vial stoppering		25°C	850 ± 50 mbar

^a Chamber pressure was controlled using sterile filtered nitrogen. The pressure was determined by instruments based on capacitance measurements.

The four reconstituted formulations were tested for stability (i) prior to lyophilisation, (ii) after immediate post-lyophilisation reconstitution, and (iii) after reconstitution following storage at 2-8°C or 40°C for four weeks. Stability was evaluated by % impurities as measured by size exclusion–High Pressure Liquid Chromatography (SEC-HPLC), Dynamic Light Scattering (DLS) and visual inspection (assessed after overnight storage at 2-8°C). The results are shown in Tables 6 to 10 below.

Table 6: Aggregation products results from SEC-HPLC

	Pre-lyophilisation	Post-lyophilisation	2-8°C for 4 weeks	40°C for 4 weeks
F1	<0.1%	<0.1%	<0.1%	0.24%
F2	<0.1%	<0.1%	<0.1%	0.18%
F3	<0.1%	<0.1%	<0.1%	0.14%
F3b	<0.1%	<0.1%	<0.1%	0.23%

Table 7: Degradation products results from SEC-HPLC

	Pre-lyophilisation	Post-lyophilisation	2-8°C for 4 weeks	40°C for 4 weeks
F1	0.15%	0.11%	0.16%	0.16%
F2	0.13%	0.14%	0.14%	0.12%
F3	0.12%	0.15%	0.13%	0.10%
F3b	0.11%	0.12%	0.15%	0.11%

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Table 8: Small particles; results for PolyDispensity Index (PDI) from Dynamic Light Scattering

	Pre-lyophilisation	Post-lyophilisation	2-8°C for 4 weeks	40°C for 4 weeks
F1	12.5%	27.5%	23.8%	23.8%
F2	12.1%	43.9%	23.5%	23.5%
F3	7.4%	19.4%	17.3%	16.1%
F3b	7.7%	22.8%	18.3%	17.8%

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Table 9: Small particles; results for particles radius (r.nm) from Dynamic Light Scattering (diluted samples)

	Pre-lyophilisation	Post-lyophilisation	2-8°C for 4 weeks	40°C for 4 weeks
F1	4.1 nm	2.9 nm	3.6 nm	4.0 nm
F2	4.2 nm	3.0 nm	4.0 nm	4.4 nm
F3	5.6 nm	5.5 nm	5.5 nm	5.7 nm
F3b	5.7 nm	5.7 nm	5.9 nm	5.7 nm

Table 10: Visual clarity

	Pre-lyophilisation	Post-lyophilisation	2-8°C for 4 weeks	40°C for 4 weeks
F1	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles
F2	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles
F3	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles
F3b	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles	Clear, no visible particles

Overall, all the formulation tested showed good results. F3 showed the lowest aggregation of MOR6654B before and after reconstitution, measured by Dynamic Light Scattering (DLS, see Table 8). Based on these results a stability study was performed with formulation F3. The reconstituted F3 formulation was prepared as described above but in a 10 L scale. Table 11 shows the stability results obtained with F3 as measured by SEC-HPLC.

Table 11: Stability of F3 as measured by SEC-HPLC

Storage Conditions Purity / Impurities [%]	Purity	Sum of aggregates	Sum of fragments
Initial analysis	99.6	0.36	<0.10
5°C 3 months	99.5	0.44	<0.10
6 months	99.5	0.45	<0.10
25°C/60% RH 3 months	99.3	0.67	<0.10
6 months	99.1	0.76	<0.10
40°C/75% RH 3 months	98.6	1.4	<0.10
6 months	98.1	1.7	0.10

CLAIMS

1. A lyophilized formulation prepared by lyophilizing an aqueous formulation having a pH of 5.0-7.0 and comprising
- 5 (i) an anti-BAFFR antibody wherein the antibody has a concentration of 20-120 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) a stabilizer,
- (iii) a buffering agent,
- 10 (iv) a surfactant, and optionally
- (v) an amino acid.
2. The lyophilized formulation of claim 1, wherein said formulation is prepared from an aqueous formulation having a pH of 5.0-7.0 and comprising
- 15 (i) an anti-BAFFR antibody wherein the antibody has a concentration of 20-120mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) sucrose or trehalose as a stabilizer,
- (iii) histidine as a buffering agent,
- 20 (iv) polysorbate 80 as a surfactant, and optionally
- (v) an amino acid selected from arginine and glycine.
3. The lyophilized formulation of claim 1, wherein said formulation is prepared from an aqueous formulation having a pH of 5.0-7.0 and comprising
- 25 (i) an anti-BAFFR antibody wherein the antibody has a concentration of 20-120 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) 3-300 mM sucrose or trehalose as a stabilizer,
- (iii) 1-60 mM histidine as a buffering agent,
- 30 (iv) up to 0.2% polysorbate 80 as a surfactant, and optionally
- (v) 2-80 mM arginine or glycine.

4. The lyophilized formulation of claim 1, wherein said formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) 90 mM sucrose as a stabilizer,
- (iii) 7 mM histidine as a buffering agent, and
- (iv) 0.02% polysorbate 80 as a surfactant.
5. The lyophilized formulation of claim 1, wherein said formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) 90 mM sucrose as a stabilizer,
- (iii) 7 mM histidine as a buffering agent,
- (iv) 0.02% polysorbate 80 as a surfactant, and
- (v) 20 mM glycine-HCl.
6. The lyophilized formulation of claim 1, wherein said formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) 90 mM sucrose as a stabilizer,
- (iii) 7 mM histidine as a buffering agent,
- (iv) 0.02% polysorbate 80 as a surfactant, and
- (v) 17 mM arginine-HCl.
7. The lyophilized formulation of claim 1, wherein said formulation is prepared from an aqueous formulation having a pH of 6.5 and comprising

- (i) an anti-BAFFR antibody wherein the antibody has a concentration of 66.6 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 5 (ii) 90 mM sucrose as a stabilizer,
- (iii) 7 mM histidine as a buffering agent,
- (iv) 0.02% polysorbate 80 as a surfactant, and
- (v) 17 mM arginine-HCl.
8. An aqueous pharmaceutical composition obtained by reconstituting a lyophilized
- 10 formulation of anyone of the preceding claims, wherein the reconstitution factor is between 1:0.5 to 1:6.
9. The aqueous pharmaceutical composition of claim 8, wherein the reconstitution factor is 1:3.
10. An aqueous pharmaceutical composition having a pH of 5.0 to 7.0 comprising
- 15 (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) a stabilizer,
- 20 (iii) a buffering agent,
- (iv) a surfactant, and optionally
- (v) an amino acid.
11. The aqueous pharmaceutical composition of claim 10 comprising
- 25 (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- (ii) sucrose or trehalose as a stabilizer,
- (iii) histidine as a buffering agent,
- 30 (iv) polysorbate 80 as a surfactant, and optionally
- (v) an amino acid selected from arginine and glycine.

12. The aqueous pharmaceutical composition of claim 10 or 11 comprising
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
 - (ii) 200-300 mM sucrose as a stabilizer,
 - (iii) 25-35 mM histidine as a buffering agent,
 - (iv) up to 0.2% polysorbate 80 as a surfactant, and optionally
 - (v) 10-80 mM arginine or glycine.
13. The aqueous pharmaceutical composition of anyone of claims 10 to 12, wherein the composition has a pH of 6.5 and comprises
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
 - (ii) 270 mM sucrose as a stabilizer,
 - (iii) 21 mM histidine as a buffering agent, and
 - (iv) 0.06% polysorbate 80 as a surfactant.
14. The aqueous pharmaceutical composition of anyone of claims 10 to 12, wherein the composition has a pH of 6.5 and comprises
- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
 - (ii) 270 mM sucrose as a stabilizer,
 - (iii) 21 mM histidine as a buffering agent,
 - (iv) 0.06% polysorbate 80 as a surfactant, and
 - (v) 60 mM glycine.
15. The aqueous pharmaceutical composition of anyone of claims 10 to 12, wherein the composition has a pH of 6.5 and comprises

- (i) an anti-BAFFR antibody wherein the antibody has a concentration of at least 50 mg/ml, and wherein said anti-BAFFR antibody includes heavy chain CDR1, CDR2 and CDR3 of SEQ ID NOs 3, 4 and 5 respectively, and light chain CDR1, CDR2 and CDR3 of SEQ ID NOs: 6, 7 and 8,
- 5 (ii) 270 mM sucrose as a stabilizer,
- (iii) 21 mM histidine as a buffering agent,
- (iv) 0.06% polysorbate 80 as a surfactant, and
- (v) 51 mM arginine.
- 10 16. The aqueous pharmaceutical composition of anyone of claims 10 to 15, wherein the BAFFR antibody has a concentration of 150 mg/ml.
17. The lyophilized formulation of anyone of claims 1 to 7 or the aqueous pharmaceutical composition of anyone of claims 8 to 16, wherein the anti-BAFFR antibody comprises a V_H domain with amino acid SEQ ID NO: 1 and a V_L domain with amino acid SEQ ID NO: 2.
- 15 18. The lyophilized formulation of anyone of claims 1 to 7 or the aqueous pharmaceutical composition of anyone of claims 8 to 16, wherein the anti-BAFFR antibody comprises a heavy chain region of SEQ ID NO: 9 and a light chain region of SEQ ID NO: 10.
19. A delivery device including the aqueous pharmaceutical composition of anyone of claims 8 to 16.
- 20 20. A pre-filled syringe including the aqueous pharmaceutical composition of anyone of claims 8 to 16.
21. A method for delivering an anti-BAFFR antibody to a mammal, comprising a step of administering to the patient an aqueous pharmaceutical composition of anyone of claims 8 to 16.
- 25 22. A lyophilized formulation of anyone of claims 1 to 7 or an aqueous pharmaceutical composition of anyone of claims 8 to 16 for use in treating a disease or disorder that is mediated by BAFF receptor or that can be treated by killing or depleting B cells.
23. The lyophilized formulation or aqueous pharmaceutical composition according to claim 22 for use in the treatment of autoimmune diseases.
- 30 24. The lyophilized formulation or aqueous pharmaceutical composition according to claim 22 for use in the treatment of B cell neoplasms, such as lymphoma, leukemia or myeloma.

25. The lyophilized formulation or aqueous pharmaceutical composition according to claim 22 for use in the treatment of rheumatoid arthritis, systemic lupus erythematosus, or Pemphigus vulgaris.