Specifically binds: The term "specifically binds" as used throughout the present specification in relation to antigen binding proteins means that the antigen binding protein binds to TNF-alpha with no or insignificant binding to other unrelated proteins. The term however does not exclude the fact that the antigen binding proteins may also be cross-reactive with closely related molecules. The antigen binding proteins described herein may bind to TNF-alpha with at least 2, at least 5, at least 10, at least 50, at least 100, or at least 1000 fold greater affinity than they bind to closely related molecules.

CDRs:

"CDRs" are defined as the complementarity determining region amino acid sequences of an antigen binding protein. These are the hypervariable regions of immunoglobulin heavy and light chains. There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, all three light chain CDRs, all heavy and light chain CDRs, or at least two CDRs.

Throughout this specification, amino acid residues in variable domain sequences and full length antibody sequences are numbered according to the Kabat numbering convention. Similarly, the terms "CDR", "CDRL1", "CDRL2", "CDRL3", "CDRH1", "CDRH2", "CDRH3" used in the Examples follow the Kabat numbering convention. For further information, see Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

% identity of variants : The term "identical" or "sequence identity" indicates the degree of identity between two nucleic acid or two amino acid sequences when optimally aligned and compared with appropriate insertions or deletions. The variants described herein may have 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity to the native CDR or variable domain sequences at the amino acid level.

It will be understood that particular embodiments described herein are shown by way of illustration and not as limitations of the invention. The principal features of this invention can be employed in various embodiments without departing from the scope of the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine study, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the claims. All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. ~~All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.~~ The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the

Claims

1. An antigen binding protein which specifically binds to TNF-alpha comprising:
(i) CDRH1 of (SEQ ID NO: 27), CDRH2 of (SEQ ID NO: 28), CDRH3 of (SEQ ID No: 29), CDRL1 of (SEQ ID NO: 30), CDRL2 of (SEQ ID NO: 31), and CDRL3 of (SEQ ID NO: 32); or a CDR variant thereof which contains 1, 2, 3 or 4 amino acid substitutions, insertions or deletions as compared to CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3; and
(ii) a neonatal Fc receptor (FcRn) binding portion of a human IgG1 constant domain comprising one of more amino acid substitutions relative to the human IgG1 constant domain wherein the one or more amino acid substitution is at amino acid residues 252, 254 and 256 numbered according to EU index of Kabat and the substitution at residue 252 is a substitution with tyr, phe, trp or thr; the substitution at residue 254 is a substitution with thr; and the substitution at residue 256 is a substitution with ser, arg, glu, asp or thr and wherein the antigen binding protein has an increased FcRn binding affinity at pH 6 and/ or increased half-life as compared to an IgG comprising the light chain sequence of SEQ ID No. 2 and the heavy chain sequence of SEQ ID No.12.

2. An antigen binding protein as claimed in any preceding claim wherein the substitution at residue 252 is a substitution of met with tyr; the substitution at residue 254 is a substitution of ser with thr and the substitution at residue 256 is a substitution of thr with glu.

3. An antigen binding protein according to claim 1 or claim 2 wherein the antigen binding protein has an increased half life as compared to an IgG comprising the light chain sequence of SEQ ID No. 2 and the heavy chain sequence of SEQ ID No.12 and the antigen binding protein can be administered no more than once every four weeks to achieve comparable mean steady-state trough concentration as that achieved by the same dose of the IgG comprising light chain sequence of SEQ ID No. 2 and heavy chain sequence of SEQ ID No.12 administered once every two weeks.

4. An antigen binding protein according to claim 1 or claim 2
wherein the antigen binding protein has an affinity for FcRn of 4 fold greater than an anti-TNF antigen binding protein with the same CDR's without such modifications at pH 6 as assessed by ProteOn XPR36 protein interaction array system at 25°C, the array system having antigen binding proteins immobilised on the chip.

5. An antigen binding protein according to claim 1 or claim 2 wherein when the antigen binding protein is administered to patients at a single dose of 40 mg at a four to eight weekly interval, the mean steady-state trough antibody concentration in the patient population does not fall below 5 µg /ml, preferably below 6 µg /ml, between dosing intervals.

62. An antigen binding protein as claimed in any preceding claim 1 wherein the human IgG1 constant domain has the sequence of SEQ ID No. 13 before amino acid substitutions are introduced.

~~7. An antigen binding protein as claimed in any one of claims 1 to 6 for use as a medicament for treating disease wherein the antigen binding protein can be administered to patients no more than once every four weeks to achieve comparable mean steady-state trough concentration as that achieved by the same dose of an IgG comprising the light chain sequence of SEQ ID No. 2 and the heavy chain sequence of SEQ ID No.12 administered once every two weeks.~~

~~8~~3. An antigen binding protein as claimed in claim in any preceding claim for treatment of a disease wherein the antigen binding protein is to be administered to patients at a single dose between about 35 to about 45 mg at a four to eight weekly interval.

~~9~~4. An antigen binding protein as claimed in claim ~~8~~ 3 wherein the antigen binding protein is to be administered to patients subcutaneously as a single 40 mg dose no more than once every four weeks.

~~10~~5. An antigen binding protein as claimed in claim ~~8~~ 3 or claim ~~9~~ 4wherein the antigen binding protein is to be administered to patients subcutaneously as a single 40 mg dose no more than once every eight weeks.

~~11~~6. An antigen binding protein as claimed in any one of claims 1 to ~~10~~ 5 wherein the half-life of the antigen binding protein is increased 2 fold, 3 fold, 4 fold or 5 fold as compared to the native IgG.

~~12~~7. An antigen binding protein as claimed in any preceding claim wherein administration of the antigen binding protein no more than once every four weeks in patients achieves the mean steady-state trough concentration in the patient population of between about 4 µg/ml to about 7 µg/ml.

~~13~~8. An antigen binding protein as claimed in claim ~~12~~ 7 wherein the mean steady-state trough concentration is between about 5 µg/ml to about 6 µg/ml.

~~14~~9. An antigen binding protein as claimed in any one of claims 1 to ~~13~~ 8 wherein the clearance of the antigen binding protein is about 2.ml/ hr to about 4ml/hr

~~15~~10. An antigen binding protein as claimed in any preceding claim comprising a constant domain as shown in SEQ ID No: 7

~~16~~11. An antigen binding protein as claimed in any one of claims 1 to ~~15~~ 10 wherein the antigen binding protein is an antibody.

~~17~~12. An antigen binding protein as claimed in any one of claims 1 to ~~16~~ 11 wherein the antigen binding protein is to be administered with methotrexate, preferably wherein the antigen binding protein is administered for the treatment of rheumatoid arthritis.

~~18~~13. An antigen binding protein as claimed in any one of claims 1 to ~~17~~ 12 comprising the heavy chain sequence as shown in SEQ ID NO 5 optionally with a light chain sequence as shown in SEQ ID No: 2.

~~19~~14. ~~A method of treating a patient with a disease, the method comprising administering an~~Use of an antigen binding protein as claimed in any preceding claim in the manufacture of a medicament for treating a patient with a disease.

~~20~~15. ~~A method of treating a patient with a disease, the method comprising administering an~~The use of claim 14, wherein the antigen binding protein ~~as claimed in any one of claims 1 to 14~~is to be administered to the patient subcutaneously as a single of dose about 35 to about 45 mg at a four to eight weekly interval.

~~21~~16. Use of an antigen binding protein as claimed in any one of claims 1 to ~~20~~ 15 for use in the manufacture of a medicament for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or Psoriasis.

~~22~~ 17 An antigen binding protein as claimed in any one of claims 1 to ~~20~~ 13 for use in the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease or Psoriasis.

~~23~~18. A nucleic acid comprising a nucleotide sequences encoding the antigen binding protein as claimed in any one of claims 1 to 13~~22~~.

~~24~~19. A host cell comprising the nucleic acid as claimed in claim ~~23~~18.