CLAIMS

1. A pharmaceutical composition comprising an agent capable of activating CD4+CD25+ regulatory T cells and methotrexate.

2. A kit comprising separately an agent capable of activating CD4+CD25+ regulatory T cells and methotrexate.

3. A pharmaceutical composition or kit according to claim 1 or claim 2 wherein the agent is suitable for parenteral administration.

4. A pharmaceutical composition or kit according to claim 3, wherein the agent is suitable for intramuscular, intravenous or subcutaneous administration.

5. A pharmaceutical composition or kit according to any preceding claim wherein the methotrexate is suitable for oral, intramuscular, intravenous or subcutaneous administration.

6. A pharmaceutical composition or kit according to any preceding claim wherein the agent capable of activating CD4+CD25+ regulatory T cells is an antibody or fragment or derivative thereof.

7. A pharmaceutical composition or kit according to claim 6 wherein the antibody is a humanized monoclonal antibody.

8. A pharmaceutical composition or kit according to claim 6 or claim 7 wherein the agent is an anti-CD4 antibody or fragment or derivative thereof.

9. A pharmaceutical composition or kit according to claim 8 wherein the agent is a humanized anti-CD4 antibody which comprises a sequence comprising the complementarity-determining regions (CDRs) of the mouse monoclonal antibody B-F5, optionally with variations in the sequence that do not substantially affect the antibody specificity and/or affinity thereof.

10. A pharmaceutical composition or kit according to claim 8 wherein the agent is a humanized anti-CD4 antibody having V domains defined by the following polypeptide sequences:

- H chain V domain:

EEQLVESGGGLVKPGGSLRLSCAASGFSFSDCRMYWLRQAPGKGLEWIGVISVKSEN YGANYAESVRGRFTISRDDSKNTVYLQMNSLKTEDTAVYYCSASYYRYDVGAWFA YWGQGTLVTVSS (SEQ ID NO: 1)

- L chain V domain:

DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSYIYWYQQKPGQPPKLLIYLASILE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQHSRELPWTFGQGTKVEIK (SEQ ID NO: 2).

or V domains comprising polypeptide sequences having at least 80% sequence identity with SEQ ID NO: 1 and SEQ ID NO: 2.

11. A pharmaceutical composition or kit according to any preceding claim wherein the agent capable of activating CD4+CD25+ regulatory T cells is to be administered to a subject in a dose from 0.2 mg to 10 mg.

12. A pharmaceutical composition or kit according to claim 11 wherein the agent capable of activating CD4+CD25+ regulatory T cells is to be administered to a subject in a dose from 0.2 mg to 5 mg.

13. A pharmaceutical composition or kit according to claim 12 wherein the agent capable of activating CD4+CD25+ regulatory T cells is to be administered to a subject in a dose from 0.5 mg to 3 mg.

14. A pharmaceutical composition according to any preceding claim wherein the composition or agent is for intravenous administration and is provided in a dosage volume of 0.5 to 500 ml or in a form for dilution to the dosage volume of 0.5 to 500 ml.

15. A pharmaceutical composition according to any one of claims 1 to 13 wherein the composition or agent is suitable for providing or provided in a dosage volume of 0.5 to 1.5 ml.

16. A pharmaceutical composition according to any one of claims 1 to 13 wherein the composition or agent is suitable for providing or provided in a dosage volume of 15 to 25 ml.

17. A pharmaceutical composition according to any one of claims 1 to 13 wherein the composition is suitable for subcutaneous or intramuscular administration and is provided in a dosage volume of 0.1 to 3 ml.

18. A pharmaceutical composition according to any preceding claim wherein the composition or agent is suitable for use as a single dose.

19. A pharmaceutical composition according to any one of claims 1 to 17 wherein the composition or agent is suitable for use as part of a plurality of doses.

20. A pharmaceutical composition according to claim 20 wherein each dose of the plurality of doses is to be administered weekly.

21. A method of treating a rheumatic disease in a patient comprising a step (a) of administering an agent capable of activating CD4+CD25+ regulatory T cells and a step (b) of administering methotrexate, wherein step (a) and step (b) can be conducted simultaneously, separately or sequentially and in either order.

22. A method of treating a rheumatic disease in a patient undergoing methotrexate treatment comprising a step of administering an agent capable of activating CD4+CD25+ regulatory T cells.

23. A method of treating a rheumatic disease in a patient undergoing treatment with an agent capable of activating CD4+CD25+ regulatory T cells comprising a step of administering methotrexate.

24. A method of treating a rheumatic disease in a patient according to any one of claims 21 to 23 wherein the rheumatic disease is selected from rheumatoid arthritis, psoriatic arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis.

25. A method of treating a rheumatic disease in a patient according to claim 24, wherein the rheumatic disease is rheumatoid arthritis.

26. A method of treating rheumatoid arthritis in a patient who is a non-responder to treatment with a disease-modifying anti-rheumatic drug (DMARD), comprising a step (a) of administering an agent capable of activating CD4+CD25+ regulatory T cells and a step (b) of administering methotrexate, wherein step (a) and step (b) can be conducted simultaneously, separately or sequentially and in either order.

27. A method of treating rheumatoid arthritis in a patient according to claim 26 wherein the DMARD is methotrexate.

28. A method of treating a rheumatic disease in a patient according to any one of claims 21 to 27 wherein the agent is administered parenterally.

29. A method of treating a rheumatic disease in a patient according to claim 28 wherein the agent is administered intramuscularly, intravenously or subcutaneously.

30. A method of treating a rheumatic disease in a patient according to any one of claims 21 to 29 wherein the methotrexate is administered orally, intramuscularly, intravenously or subcutaneously.

31. A method of treating a rheumatic disease in a patient according to any one of claims 21 to 30 wherein the agent is administered to the patient in an amount from 0.2 to 10 mg.

32. A method of treating a rheumatic disease in a patient according to claim 31 wherein the agent is administered to the patient in an amount from 0.2 to 5 mg.

33. A method of treating a rheumatic disease in a patient according to claim 32 wherein the agent is administered to the patient in an amount from 0.5 to 3 mg.

34. A method of treatment according to claim 31 wherein the agent is administered intravenously and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of the administration is less than 2.5 μg/ml.

35. A method of treatment according to claim 32 wherein the agent is administered intravenously and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of the administration is less than 0.3 μg/ml.

36. A method of treatment according to claim 33 wherein the agent is administered intravenously and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of the administration is less than 0.1 μg/ml.

37. A method of treatment according to claim 31 wherein the agent is administered intravenously once every week and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of the second administration is less than 2.5 μg/ml.

38. A method of treatment according to claim 32 wherein the agent is administered intravenously once every week and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of the second administration is less than 0.3 μg/ml.

39. A method of treatment according to claim 33 wherein the agent is administered intravenously once every week and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of the second administration is less than 0.1 μg/ml.

40. A method of treatment according to claim 31 wherein the agent is administered intravenously once every week and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of any administration is less than 2.5 μg/ml.

41. A method of treatment according to claim 32 wherein the agent is administered intravenously once every week and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of any administration is less than 0.3 μg/ml.

42. A method of treatment according to claim 33 wherein the agent is administered intravenously once every week and wherein the maximum concentration of the agent in the patient's plasma 3 hours after the end of any administration is less than 0.1 μg/ml.

43. A method of treating a rheumatic disease in a patient according to any one of claims 21 to 30 wherein the agent is administered to the patient in an amount from 2 to 150 μg/kg.

44. A method of treating a rheumatic disease in a patient according to claim 43 wherein the agent is administered to the patient in an amount from 2 to 75 μg/kg.

45. A method of treating a rheumatic disease in a patient according to claim 44 wherein the agent is administered to the patient in an amount from 5 to 45 μg/kg.

46. A method of treating a rheumatic disease in a patient according to any one of claims 21 to 30 wherein the agent is administered to the patient in an amount from 0.1 to 5 mg/m^2 body surface area of the patient.

47. A method of treating a rheumatic disease in a patient according to claim 46 wherein the agent is administered to the patient in an amount from 0.1 to 2.5 mg/m^2 body surface area of the patient.

48. A method of treating a rheumatic disease in a patient according to claim 47 wherein the agent is administered to the patient in an amount from 0.25 to 1.5 mg/m^2 body surface area of the patient.

49. A method of treating a rheumatic disease according to any one of claims 21 to 48 wherein a single dose of the agent is administered to the patient.

50. A method of treating a rheumatic disease according to any one of claims 21 to 48 wherein a plurality of doses of the agent are administered to the patient.

51. A method of treating a rheumatic disease according to claim 50 wherein the agent and/or the methotrexate are administered at most every week.

52. A method of treating a rheumatic disease according to claim 51 wherein the agent and/or the methotrexate are administered every two weeks, every three weeks or every four weeks.

53. A method of treating a rheumatic disease according to any one of claims 21 to 52 which comprises a further step of administering an additional therapeutic agent suitable for treating the disease, selected from a non-steroidal anti-inflammatory drug, an anti-

inflammatory steroid, a gold compound, an anti-malarial drug, folic acid, cyclosporine, leflunomide, azathioprine, sulfasalazine, d-penicillamine, cyclophosphamide, mycophenoate, minocycline and chlorambucil.

54. A method of treating a rheumatic disease according to any one of claims 21 to 53 wherein the rheumatic disease is rheumatoid arthritis and wherein the treatment provides an improvement of the disease in the patient of at least ACR50 according to the American College of Rheumatology (ACR) scoring system.

55. A method of treating a rheumatic disease according to claim 54 wherein the treatment provides an improvement of the disease in the patient of at least ACR70 according to the American College of Rheumatology (ACR) scoring system.

56. A method of treating a rheumatic disease according to claim 55 wherein the treatment provides at least an ACR 70 response in the patient between 6 to 8 weeks after the start of treatment.

57. An agent capable of activating CD4+CD25+ regulatory T cells and methotrexate as a combined preparation for simultaneous, separate or sequential use in medicine.

58. An agent capable of activating CD4+CD25+ regulatory T cells and methotrexate as a combined preparation for simultaneous, separate or sequential use according to claim 57 in the treatment of a rheumatic disease.

59. Use of an agent capable of activating CD4+CD25+ regulatory T cells and methotrexate for the manufacture of a combined preparation for simultaneous, separate or sequential use in the treatment of a rheumatic disease in a patient.

60. An agent capable of activating CD4+CD25+ regulatory T cells for use in the treatment of a rheumatic disease in a patient, wherein the patient is undergoing methotrexate treatment.

61. A composition comprising methotrexate for use in the treatment of a rheumatic disease in a patient, wherein the patient is undergoing treatment with an agent capable of activating CD4+CD25+ regulatory T cells.

62. Use according to any one of claims 58 to 61 wherein the rheumatic disease is selected from rheumatoid arthritis, psoriatic arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis.

63. Use according to claim 62 wherein the rheumatic disease is rheumatoid arthritis.

64. An agent capable of activating CD4+CD25+ regulatory T cells and methotrexate as a combined preparation for simultaneous, separate or sequential use according to claim 57 in the treatment of a rheumatic disease in a patient who is a non-responder to treatment with a disease modifying anti-rheumatic drug (DMARD).

65. An agent for use according to claim 64 wherein the DMARD is methotrexate.

66. Use according to any one of claim 57 to 65 wherein the agent is suitable for parenteral administration.

67. Use according to claim 66 wherein the agent is suitable for intramuscular, intravenous or subcutaneous administration.

68. Use according to any one of claim 57 to 67 wherein the methotrexate is suitable for oral, intramuscular, intravenous or subcutaneous administration.

69. Use according to any one of claims 57 to 68 wherein the agent is to be administered to the patient in an amount from 0.2 to 10 mg.

70. Use according to claim 69 wherein the agent is suitable for intravenous administration and is capable of establishing a maximum concentration in the patient's plasma of less than 2.5 μg/ml 3 hours after administration.

71. Use according to any one of claims 57 to 68 wherein the agent is to be administered to the patient in an amount from 2 to 150 μg/kg.

72. Use according to any one of claims 57 to 68 wherein the agent is to be administered to the patient in an amount from 0.1 to 5 mg/m^2 body surface area of the patient.

73. Use according to any one of claims 57 to 72 wherein the agent is suitable for administration as a single dose.

74. Use according to any one of claims 57 to 72 wherein the agent is suitable for administration as part of a plurality of doses.

75. Use according to claim 74 wherein the agent is suitable for administration at most once every week.

76. Use according to any one of claims 57 to 72 wherein the combined preparation further comprises an additional therapeutic agent suitable for treating the disease, selected from a non-steroidal anti-inflammatory drug, an anti-inflammatory steroid, a gold compound, an anti-malarial drug, folic acid, cyclosporine, leflunomide, azathioprine, sulfasalazine, d-penicillamine, cyclophosphamide, mycophenoate, minocycline and chlorambucil.

77. Use according to any one of claims 58 to 76 wherein the rheumatic disease is rheumatoid arthritis and wherein the combined preparation is capable of providing an improvement of the disease in the patient of at least ACR50 according to the American College of Rheumatology (ACR) scoring system.

78. A method or use according to any one of claims 21 to 77 wherein the agent capable of activating CD4+CD25+ regulatory T cells is an antibody or fragment or derivative thereof.

79. A method or use according to claim 78 wherein the antibody is a humanized monoclonal antibody.

80. A method or use according to claim 78 or claim 79 wherein the agent is an anti-CD4 antibody or fragment or derivative thereof.

81. A method or use according to claim 80 wherein the agent is a humanized anti-CD4 antibody which comprises a sequence comprising the complementarity-determining regions (CDRs) of the mouse monoclonal antibody B-F5, optionally with variations in the sequence that do not substantially affect the antibody specificity and/or affinity thereof.

82. A method or use according to claim 80 wherein the agent is a humanized anti-CD4 antibody having V domains defined by the following polypeptide sequences:

- H chain V domain:

EEQLVESGGGLVKPGGSLRLSCAASGFSFSDCRMYWLRQAPGKGLEWIGVISVKSEN YGANYAESVRGRFTISRDDSKNTVYLQMNSLKTEDTAVYYCSASYYRYDVGAWFA YWGQGTLVTVSS (SEQ ID NO: 1)

- L chain V domain:

DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSYIYWYQQKPGQPPKLLIYLASILE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQHSRELPWTFGQGTKVEIK (SEQ ID NO: 2).

or V domains comprising polypeptide sequences having at least 80% sequence identity with SEQ ID NO: 1 and SEQ ID NO: 2.

83. A method comprising preparing a pharmaceutical composition or kit comprising the agent and the methotrexate according to any one of claims 1 to 20.

CLAIMS

1. A pharmaceutical composition comprising an agent capable of activating CD4+CD25+ regulatory T cells and methotrexate,

wherein the agent is a humanized anti-CD4 antibody which comprises an H chain V domain and an L chain V domain, and wherein: (a) the H chain V domain comprises the sequences DCRMY, VISVKSENYGANYAESVRG and SYYRYDVGAWFAY, and the L chain V domain comprises the sequences RASKSVSTSGYSYIY, LASILES and QHSRELPWT; or (b) the H chain V domain has at least 80% sequence identity with SEQ ID No: 1 and the L chain V domain has at least 80% sequence identity with SEQ ID No: 2.

2. Use of an agent capable of activating CD4+CD25+ regulatory T cells and methotrexate for the manufacture of a combined preparation for simultaneous, separate or sequential use in the treatment of a rheumatic disease in a patient,

wherein the agent is a humanized anti-CD4 antibody which comprises an H chain V domain and an L chain V domain, and wherein: (a) the H chain V domain comprises the sequences DCRMY, VISVKSENYGANYAESVRG and SYYRYDVGAWFAY, and the L chain V domain comprises the sequences RASKSVSTSGYSYIY, LASILES and QHSRELPWT; or (b) the H chain V domain has at least 80% sequence identity with SEQ ID No: 1 and the L chain V domain has at least 80% sequence identity with SEQ ID No: 2.

3. Use of an agent capable of activating CD4+CD25+ regulatory T cells for the manufacture of a medicament for treating a rheumatic disease in a patient, wherein the patient is undergoing methotrexate treatment,

wherein the agent is a humanized anti-CD4 antibody which comprises an H chain V domain and an L chain V domain, and wherein: (a) the H chain V domain comprises the sequences DCRMY, VISVKSENYGANYAESVRG and SYYRYDVGAWFAY, and the L chain V domain comprises the sequences RASKSVSTSGYSYIY, LASILES and QHSRELPWT; or (b) the H chain V domain has at least 80% sequence identity with SEQ ID No: 1 and the L chain V domain has at least 80% sequence identity with SEQ ID No: 2.

4. Use of methotrexate for the manufacture of a medicament for treating a rheumatic disease in a patient, wherein the patient is undergoing treatment with an agent capable of activating CD4+CD25+ regulatory T cells,

wherein the agent is a humanized anti-CD4 antibody which comprises an H chain V domain and an L chain V domain, and wherein: (a) the H chain V domain comprises the sequences DCRMY, VISVKSENYGANYAESVRG and SYYRYDVGAWFAY, and the L chain V domain comprises the sequences RASKSVSTSGYSYIY, LASILES and QHSRELPWT; or (b) the H chain V domain has at least 80% sequence identity with SEQ ID No: 1 and the L chain V domain has at least 80% sequence identity with SEQ ID No: 2.

5. Use of an agent capable of activating CD4+CD25+ regulatory T cells for the manufacture of a medicament for treating rheumatoid arthritis in a patient, wherein the patient is a non-responder to treatment with a disease modifying anti-rheumatic drug (DMARD),

wherein the patient is to receive methotrexate, wherein the agent is a humanized anti-CD4 antibody which comprises an H chain V domain and an L chain V domain, and wherein: (a) the H chain V domain comprises the sequences DCRMY, VISVKSENYGANYAESVRG and SYYRYDVGAWFAY, and the L chain V domain comprises the sequences RASKSVSTSGYSYIY, LASILES and QHSRELPWT; or (b) the H chain V domain has at least 80% sequence identity with SEQ ID No: 1 and the L chain V domain has at least 80% sequence identity with SEQ ID No: 2.

6. Use according to claim 5, wherein the DMARD is methotrexate.

7. Use according to any one of claims 2 to 4 wherein the rheumatic disease is selected from rheumatoid arthritis, psoriatic arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis.

8. Use according to claim 7 wherein the rheumatic disease is rheumatoid arthritis.

9. A pharmaceutical composition according to claim 1 or use according to any one of claim 2 to 8, wherein the agent is for parenteral administration.

10. A pharmaceutical composition or use according to claim 9 wherein the agent is for intramuscular, intravenous or subcutaneous administration.

11. A pharmaceutical composition according to any one of claims 1, 9 or 10 or use according to any one of claims 2 to 10, wherein the agent is to be administered to the patient:

(i) intravenously in a dose from 0.2 to 10 mg; from 2 to 150 μg/kg of body weight; from 0.1 to 5 mg/m^2 of body surface area, or

(ii) subcutaneously or intramuscularly in a dose from 20 to 80 mg; from 8 to 50 mg/m^2 of body surface area; or from 0.2 to 1.5 mg/kg of body weight.

12. A pharmaceutical composition according to any one of claims 1 and 9 to 11 or use according to any one of claims 2 to 11, wherein the composition or the agent is:

for intravenous administration and is provided in a dosage volume of 0.5 to 500 ml, or

for subcutaneous or intramuscular administration and is provided in a dosage volume of 0.1 to 3 ml, or 15 to 25 ml.

13. A pharmaceutical composition according to any one of claims 1 and 9 to 12 or use according to any one of claims 2 to 12 wherein the agent is for administration as a single dose or as part of a plurality of doses.

14. A pharmaceutical composition or use according to claim 13 wherein the agent is for administration at most once every week. every two weeks, every three weeks or every four weeks.

15. A pharmaceutical composition according to any one of claims 1 and 9 to 14 or use according to any one of claims 2 to 14, wherein the humanized anti-CD4 antibody comprises an H chain V domain having at least 95% sequence identity with SEQ ID No: 1 and an L chain V domain having at least 95% sequence identity with SEQ ID No: 2.

16. A pharmaceutical composition according to any one of claims 1 and 9 to 15 or use according to any one of claims 2 to 15, wherein the humanized anti-CD4 antibody has V domains defined by the following polypeptide sequences:

- H chain V domain:

EEQLVESGGGLVKPGGSLRLSCAASGFSFSDCRMYWLRQAPGKGLEWIGVISVKSEN YGANYAESVRGRFTISRDDSKNTVYLQMNSLKTEDTAVYYCSASYYRYDVGAWFA YWGQGTLVTVSS (SEQ ID NO: 1)

- L chain V domain:
DIVMTQSPDSLAVSLGERATINCRASKSVSTSGYSYIYWYQQKPGQPPKLLIYLASILE SGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQHSRELPWTFGQGTKVEIK (SEQ ID NO: 2).

17. A method comprising preparing a pharmaceutical composition comprising the agent and the methotrexate according to claim 1.

18. Use of a humanized anti-CD4 antibody for the manufacture of a medicament for treating rheumatoid arthritis in a patient, wherein the patient is undergoing methotrexate treatment, wherein the humanized anti-CD4 antibody has an H chain V domain defined by SEQ ID NO: 1, an L chain V domain defined by SEQ ID NO: 2 and an IgG1 constant domain.