CLAIMS

1. A method of assessing the appropriate therapeutic dose of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid to administer to a patient in need thereof, comprising the steps of:
   (i) testing whether or not the patient has the poor metabolizer genotype; and
   (ii) if the patient does not have the poor metaboliser genotype, administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient at the standard therapeutic dose; or
   (iii) if the patient does have the poor metaboliser genotype, either
      (a) administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient at a therapeutic dose below that of the standard therapeutic dose; or
      (b) not administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient.

2. A method of treating a patient in need with 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, comprising the steps of:
   (i) testing whether or not the patient has the poor metabolizer genotype; and
   (ii) if the patient does not have the poor metaboliser genotype, administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient at the standard therapeutic dose; or
   (iii) if the patient does have the poor metaboliser genotype, administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof,

to the patient at the standard therapeutic dose in combination with a CYP2C9 metabolic activity promoter.

3. A method of treating a patient in need with 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, comprising the steps of:

(i) testing whether or not the patient has the poor metabolizer genotype; and

(ii) if the patient does not have the poor metaboliser genotype, administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient at the standard therapeutic dose with a certain level of patient monitoring by a medical practitioner;

or

(iii) if the patient does have the poor metaboliser genotype, administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient at the standard therapeutic dose, with an increased level of patient monitoring by a medical practitioner.

4. A method of initiating use of a drug recommended not to be used with 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, comprising the steps of:

(i) testing whether or not the patient has the poor metaboliser genotype; and

(ii) if the patient does not have the poor metaboliser genotype, inititiating use of the drug within a set period after the last dose of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid or a pharmaceutically acceptable salt thereof, has been administered to the patient; or

(iii) if the patient does have the poor metaboliser genotype genotype, inititiating use of the drug within a period longer than the set period of step (ii) above after the last dose of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a

pharmaceutically acceptable salt thereof, has been administered to the patient.

5. The method of any one of claims 1 to 4, wherein the poor metabolizer genotype is the CYP2C9*3*3 and CYP2C9*2*3 genotypes.

6. The method of claim 5, wherein the the poor metaboliser genotype is the CYP2C9*3*3 genotype.

7. The method of any one of claims 1 to 3 or 5-6, wherein the daily standard therapeutic dose is in the range from 1.5 to 2.5 mg.

8. The method of claim 7, wherein the daily standard therapeutic dose is 2mg.

9. The method according to any one of claims 1 to 8, wherein the patient is suffering from multiple sclerosis.

10. The method according to claim 9, wherein the multiple sclerosis is secondary progressive multiple sclerosis with relapses (rSPMS) or secondary progressive multiple sclerosis without relapses (SPMS).

11. The method according to claim 4, wherein the set period of step (ii) is in the range from 3-14 days.

12. A method for the treatment of an autoimmune condition in a patient in need thereof, said patient having the poor metabolizer genotype, comprising administering 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, to the patient in a daily amount in the range from 0.25 – 0.75mg.

13. The method of claim 12, wherein the poor metaboliser genotype is the CYP2C9*3*3 genotype.

14. The method of claim 12 or 13, wherein the daily amount is a therapeutic dosage of 0.5mg.

15. The method of any one of claims 12 to 14, wherein the autoimmune condition is multiple sclerosis.

16. The method of claim 15, wherein the multiple sclerosis is multiple sclerosis with relapses (rSPMS) or secondary progressive multiple sclerosis without relapses (SPMS).

17. A pharmaceutical combination comprising (a) 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof; and (b) a CYP2C9 metabolic activity promoter for simultaneous, separate or sequential use.

18. A method of optimizing the daily dosage of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof to patient in need, said method comprising the steps of:

(i) measuring the patient blood lymphocyte level following administration of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof at a dose of about 2mg per day; and

(ii) in cases where the blood lymphocyte level is reduced below a level of 0.2x10e9/L following daily administration of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof at the therapeutic dosage, reducing the the daily dosage to about 1mg per day.

19. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in a method of treating an autoimmune disease, said method being according to any of claims 1-18.

20. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an autoimmune disease, said method being according to any of claims 1-18.

CLAIMS

1. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of an autoimmune disease, wherein:

   if the patient to be treated does have a poor metaboliser genotype selected from the subtypes of the CYP2C9 poor metabolizer genotype, either

   (a) 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, is to be administered to the patient at a therapeutic dose below that of the standard therapeutic dose; or

   (b) 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, is not to be administered to the patient

2. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of an autoimmune disease, wherein: if the patient to be treated does have a poor metaboliser genotype selected from the subtypes of the CYP2C9 poor metabolizer genotype, 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, is to be administered to the patient at the standard therapeutic dose in combination with a CYP2C9 metabolic activity promoter.

3. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of an autoimmune disease, wherein:

   if the patient to be treated does have a poor metaboliser genotype selected from the subtypes of the CYP2C9 poor metabolizer genotype, 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, is to be administered to the patient at the standard therapeutic dose, with an increased level of patient monitoring by a medical practitioner.

4. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, and a drug recommended not to be used with 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of an autoimmune disease, wherein:

(i) if the patient to be treated does not have the poor metaboliser genotype, the drug recommended not to be used with 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, is to be administered within a set period after the last dose of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid or a pharmaceutically acceptable salt thereof, has been administered to the patient; or

(ii) if the patient to be treated does have the poor metaboliser genotype, the drug recommended not to be used with 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, is to be administered within a period longer than the set period of step (ii) above after the last dose of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, has been administered to the patient; and

wherein the poor metabolizer genotype is selected from the subtypes of the CYP2C9 poor metabolizer genotype

5. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 4, wherein the poor metabolizer genotype is the CYP2C9*3*3 and CYP2C9*2*3 genotypes.

6. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 5, wherein the poor metaboliser genotype is the CYP2C9*3*3 genotype.

7. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to any one

of claims 1 to 3 or 5-6, wherein the daily standard therapeutic dose is in the range from 1.5 to 2.5 mg.

8. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 7, wherein the daily standard therapeutic dose is 2mg.

9. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 1 to 8, wherein the autoimmune disease is multiple sclerosis.

10. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 9, wherein the multiple sclerosis is secondary progressive multiple sclerosis with relapses (rSPMS) or secondary progressive multiple sclerosis without relapses (SPMS).

11. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 4, wherein the set period of step (ii) is in the range from 3-14 days.

12. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use in the treatment of an autoimmune disease in a patient having the poor metaboliser genotype selected from the subtypes of the CYP2C9 poor metabolizer genotype in a daily amount in the range from 0.25 – 0.75mg.

13. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 12, wherein the poor metaboliser genotype is the CYP2C9*3*3 genotype.

14. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 12 or 13, wherein the daily amount is a therapeutic dosage of 0.5mg.

15. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to any one of claims 12 to 14, wherein the autoimmune condition is multiple sclerosis.

16. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, for use according to claim 15, wherein the multiple sclerosis is multiple sclerosis with relapses (rSPMS) or secondary progressive multiple sclerosis without relapses (SPMS).

17. A pharmaceutical combination comprising (a) 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof; and (b) a CYP2C9 metabolic activity promoter for simultaneous, separate or sequential use.

18. 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof for use in the treatment of an autoimmune disease, wherein:
    (i) 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof is to be administered at a dose of about 2mg per day if the blood lymphocyte level of the patient is above 0.2x10e9/L; and
    (ii) 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof is to be administered at a daily dosage reduced to about 1mg per day, if the blood lymphocyte level of the patient is reduced below a level of 0.2x10e9/L following daily administration of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof at the therapeutic dosage.

19. Use of 1-{4-[1-(4-cyclohexyl-3-trifluoromethyl-benzyloxyimino)-ethyl]-2-ethyl-benzyl}-azetidine-3-carboxylic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of an autoimmune disease, said treatment being according to any of claims 1-18.