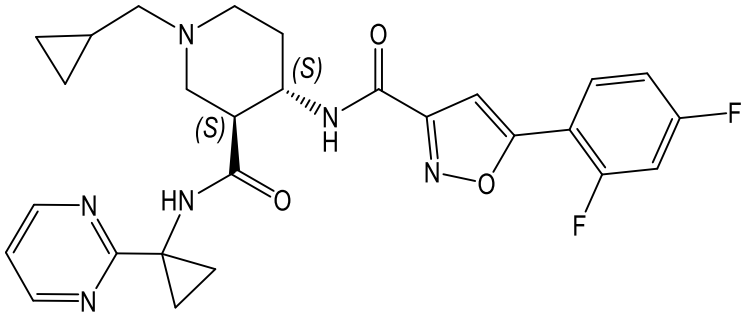
Claims

1. A a pharmaceutical composition comprising, as active principles,

- (3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide:



, or a pharmaceutically acceptable salt thereof,

- in combination with an S1P1 receptor modulator, or a pharmaceutically acceptable salt thereof,

as well as at least one pharmaceutically acceptable excipient.

2. A pharmaceutical composition according to claim 1, wherein said S1P1 receptor modulator is fingolimod, ponesimod, siponimod, ozanimod, cenerimod, or etrasimod; or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition according to claim 1 or 2, wherein said S1P1 receptor modulator, or a pharmaceutically acceptable salt thereof, is comprised in a dose of said S1P1 receptor modulator which is a tolerated efficacious dose or lower than a tolerated efficacious dose of said S1P1 receptor modulator when given as a single therapy.

4. Use of (3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combination use in the prevention or treatment of an autoimmune or inflammatory disease or disorder, a transplant rejection, or a neurodegenerative disease or disorder; wherein (3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide is ~~intended~~ to be administered in combination with an S1P1 receptor modulator, or a pharmaceutically acceptable salt thereof.

5. ~~(3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~ The use according to claim 4; wherein such use is for the prevention or treatment of

- an autoimmune and/or inflammatory disease and disorder; wherein said disease or disorder is
  - an autoimmune and/or inflammatory demyelinating disease or disorder selected from multiple sclerosis (MS); idiopathic inflammatory demyelinating diseases; neuromyelitis optica spectrum diseases including neuromyelitis optica and acute optic neuritis; auto-immune

encephalomyelitis including acute disseminated encephalomyelitis (ADEM) and multiphasic disseminated encephalomyelitis (MDEM); myelitis including transverse myelitis spectrum disorders, acute flaccid myelitis, poliomyelitis, leukomyelitis, and meningococcal myelitis; brain stem encephalitis; anti-myelin oligodendrocyte glycoprotein (anti-MOG) associated diseases including anti-MOG encephalomyelitis; Guillain–Barré syndrome; chronic inflammatory demyelinating polyneuropathy (CIDP); and anti-myelin-associated glycoprotein (anti-MAG) peripheral neuropathy;

- rheumatoid arthritis (RA);
- an inflammatory bowel disease (IBD) including Crohn's disease or ulcerative colitis;
- systemic lupus erythematosus (SLE) including lupus nephritis and neuropsychatric systemic lupus erythematosus;
- interstitial cystitis;
- celiac disease;
- osteoarthritis;
- psoriasis;
- type I diabetes;
- ankylosing spondylitis; or
- cytokine release syndrome following a strong viral infection or acute respiratory distress syndrome including COVID-19;

- a transplant rejection; wherein said transplant rejection especially is rejection of a transplanted organ such as kidney, liver, heart, lung, pancreas, cornea, or skin; graft-versus-host disease brought about by hematopoietic stem cell transplantation; chronic allograft rejection and chronic allograft vasculopathy; or
- a neurodegenerative disease and disorder; wherein said neurodegenerative disease and disorder especially is amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease (AD), Parkinson's disease (PD), or adrenoleukodystrophy.

6. (~~3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~The use according to claim 5; wherein said combination use is for the prevention or treatment of an autoimmune and/or inflammatory disease or disorder.

7. (~~3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~The use according to claim 6; wherein such use is for the treatment of a patient diagnosed with an autoimmune and/or inflammatory disease or disorder, wherein said treatment reduces the rate of progression of said autoimmune and/or inflammatory disease or disorder.

8. (~~3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~The use according to claim 7 wherein said autoimmune and/or inflammatory disease or disorder is

- an autoimmune and/or inflammatory demyelinating disease or disorder selected from multiple sclerosis (MS); idiopathic inflammatory demyelinating diseases; auto-immune encephalomyelitis including acute disseminated encephalomyelitis (ADEM) and multiphasic disseminated encephalomyelitis (MDEM); myelitis including transverse myelitis spectrum disorders, acute flaccid myelitis, poliomyelitis, leukomyelitis, and meningococcal myelitis; brain stem encephalitis; Guillain–Barré syndrome; chronic inflammatory demyelinating polyneuropathy (CIDP); anti-myelin-associated glycoprotein (anti-MAG) peripheral neuropathy; and myelin oligodendrocyte glycoprotein (MOG)-antibody associated disease;
- an inflammatory bowel disease especially selected from Crohn's disease and ulcerative colitis; or
- systemic lupus erythematosus (SLE).

9. (~~3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~The use according to claim 4, wherein such use is for the prevention or treatment of an autoimmune and/or inflammatory demyelinating disease or disorder.

10. ~~(3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~The use according to claim 9; wherein such use is

- for the treatment of a patient diagnosed with MS, wherein said treatment
  - reduces the rate of progression of MS; and/or
  - improves the symptoms of MS; and/or
  - reduces the rate of demyelination; and/or
  - reduces the rate of irreversible neurodegenerative damage such as axonal damage; and/or
  - has an effect of remyelination; and/or
  - reduces the rate of brain atrophy/cerebral atrophy; or
- for the prevention of MS, wherein said prevention of MS comprises delaying the onset of MS in a subject who is at risk / has been diagnosed as being at risk of developing MS; wherein said subject is especially a subject who has experienced a Clinically Isolated Syndrome (CIS) or has been diagnosed as having experienced a CIS.

11. ~~(3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~ The use according to any one of claims 4 to 10; wherein said S1P1 receptor modulator is fingolimod, ponesimod, siponimod, ozanimod, cenerimod, or etrasimod; or a pharmaceutically acceptable salt thereof.

12. ~~(3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for combination~~ The use according to claim 11; wherein said S1P1 receptor modulator, or a pharmaceutically acceptable salt thereof, is to be administered in a pharmaceutical dosage form suitable for the oral administration of said S1P1 receptor modulator, wherein

- fingolimod, or a pharmaceutically acceptable salt thereof, if present, is to be administered in said pharmaceutical dosage form in a unit dose suitable for the oral administration of a total of about 0.5 mg or below per day of fingolimod;
- siponimod, or a pharmaceutically acceptable salt thereof, if present, is to be administered in said pharmaceutical dosage form in a unit dose suitable for the oral administration of a total of about 2 mg or below per day of siponimod;
- ponesimod, or a pharmaceutically acceptable salt thereof, if present, is to be administered in said pharmaceutical dosage form in a unit dose suitable for the oral administration of a total of about 20 mg or below per day of ponesimod; and
- ozanimod, or a pharmaceutically acceptable salt thereof, if present, is to be administered in said pharmaceutical dosage form in a unit dose suitable for the oral administration of a total of about 1 mg or below per day of ozanimod;
- cenerimod, or a pharmaceutically acceptable salt thereof, if present, is to be administered in said pharmaceutical dosage form in a unit dose suitable for the oral administration of a total of about 4 mg or below per day of cenerimod; and
- etrasimod, or a pharmaceutically acceptable salt thereof, if present, is to be administered in said pharmaceutical dosage form in a unit dose suitable for the oral administration of a total of about 2 mg or below per day of etrasimod.

13. ~~(3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof, for~~The use according to any one of claims 4 to 12; wherein said S1P1 receptor modulator, or a pharmaceutically acceptable salt thereof, is to be administered in a dose which is a tolerated efficacious dose when given as a single therapy; or in a dose which is lower than such tolerated efficacious dose when given as a single therapy.

14. An S1P1 receptor modulator which is fingolimod, ponesimod, siponimod, ozanimod, cenerimod, or etrasimod; or a pharmaceutically acceptable salt thereof, for combination use as defined in any one of claims 4 to 13; wherein said S1P1 receptor modulator is intended to be administered in combination with (3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or a pharmaceutically acceptable salt thereof.

~~**15.** A method for the prophylaxis or treatment of an autoimmune or inflammatory disease or disorder, a transplant rejection, or a neurodegenerative disease or disorder; said method comprising the administration of~~

~~a pharmaceutically effective amount of (3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide, or of a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein (3S,4S)-1-Cyclopropylmethyl-4-{[5-(2,4-difluoro-phenyl)-isoxazole-3-carbonyl]-amino}-piperidine-3-carboxylic acid (1-pyrimidin-2-yl-cyclopropyl)-amide is administered in combination with an S1P1 receptor modulator, or a pharmaceutically acceptable salt thereof.~~