

CLAIMS

What is claimed is:

1. Use of an anti-Sortilin antibody in the manufacture of a medicament for the treatment and/or delay of progression of a disease or injury in an individual, wherein the medicament is to be administered ~~A method of treating and/or delaying the progression of a disease or injury in an individual, comprising administering to the individual an anti-Sortilin antibody intravenously at a dose of at least about 30 mg/kg once every four weeks or more frequently, wherein the antibody comprises~~ comprising:
 - (i) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYW (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and the HVR-H3 comprising the amino acid sequence ARQGSIQGGYYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);
 - (ii) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYW (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIQGGYYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRVS (SEQ ID NO: 30), and the HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);
 - (iii) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYW (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLES (SEQ ID NO: 3), the HVR-H3 comprising the amino acid sequence ARQGSIQGGYYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);
 - (iv) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYW (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIQGGYYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the

HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

(v) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32);

(vi) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33);

(vii) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIQGYYGMDV (SEQ ID NO: 5); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQSLLHSNGYNYLD (SEQ ID NO: 26), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQETPLT (SEQ ID NO: 33); or

(viii) a heavy chain variable region comprising the HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), the HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), the HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and a light chain variable region comprising the HVR-L1 comprising the amino acid sequence RSSQGLLSNGYNYLD (SEQ ID NO: 27), the HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and the HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).

2. The ~~method~~ use of claim 1, wherein the dose is at least about 35 mg/kg, at least about 40 mg/kg, at least about 45 mg/kg, at least about 50 mg/kg, at least about 55 mg/kg, or at least about 60 mg/kg.

3. The ~~method~~use of claim 1, wherein the dose is between about 30 mg/kg and about 60 mg/kg.
4. The ~~method~~use of claim 1, wherein the dose is about 60 mg/kg.
5. The ~~method~~use of any one of claims 1-4, wherein the anti-Sortilin antibody is to be administered once every two weeks.
6. The use ~~method~~ of any one of claims 1-4, wherein the anti-Sortilin antibody is to be administered once every three weeks.
7. The use ~~method~~ of any one of claims 1-4, wherein the anti-Sortilin antibody is to be administered once every four weeks.
8. The use ~~method~~ of claim 1, wherein the anti-Sortilin antibody is to be administered once every four weeks at a dose of about 60 mg/kg.
9. The use ~~method~~ of any one of claims 1-8, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSNGYNYLD (SEQ ID NO: 8), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).
10. The use ~~method~~ of any one of claims 1-8, wherein the heavy chain variable region comprises an HVR-H1 comprising the amino acid sequence YSISSGYYWG (SEQ ID NO: 1), an HVR-H2 comprising the amino acid sequence TIYHSGSTYYNPSLKS (SEQ ID NO: 2), and an HVR-H3 comprising the amino acid sequence ARQGSIKQGYYGMDV (SEQ ID NO: 6); and the light chain variable region comprises an HVR-L1 comprising the amino acid sequence RSSQSLLRSTGYNYLD (SEQ ID NO: 9), an HVR-L2 comprising the amino acid sequence LGSNRAS (SEQ ID NO: 29), and an HVR-L3 comprising the amino acid sequence MQQQEAPLT (SEQ ID NO: 32).
11. The use ~~method~~ of any one of claims 1-8, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region

comprising the amino acid sequence of SEQ ID NO: 57; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 59; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 58; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 77; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78; a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 54, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 79; or a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80.

12. The ~~use method~~ of any one of claims 1-8, wherein the antibody comprises:
 - (i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 57; or
 - (ii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 56, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 60.
13. The ~~use method~~ of any one of claims 1-12, wherein the antibody is an IgG1 isotype and the Fc region comprises amino acid substitutions at positions L234A, L235A, and P331S, wherein the numbering of the residue position is according to EU numbering.
14. The ~~use method~~ of any one of claims 1-13, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 90 or SEQ ID NO: 91, and a light chain comprising the amino acid sequence of SEQ ID NO: 95.
15. The ~~use method~~ of any one of claims 1-14, wherein the disease or injury is selected from the group consisting of frontotemporal dementia, progressive supranuclear palsy, Alzheimer's

disease, vascular dementia, seizures, retinal dystrophy, amyotrophic lateral sclerosis, traumatic brain injury, a spinal cord injury, dementia, stroke, Parkinson's disease, acute disseminated encephalomyelitis, retinal degeneration, age related macular degeneration, glaucoma, multiple sclerosis, septic shock, bacterial infection, arthritis, and osteoarthritis.

16. The ~~use method~~ of any one of claims 1-14, wherein the disease or injury is frontotemporal dementia or amyotrophic lateral sclerosis.
17. The ~~use method~~ of any one of claims 1-16, wherein the individual is heterozygous for a mutation in *GRN*.
18. The ~~use method~~ of claim 17, wherein the mutation in *GRN* is a loss-of-function mutation.
19. The ~~use method~~ of any one of claims 1-16, wherein the individual is heterozygous for a *C9orf72* hexanucleotide repeat expansion.
20. The ~~use method~~ of any one of claims 17-19, wherein the individual shows symptoms of frontotemporal dementia.
21. The ~~use method~~ of any one of claims 17-19, wherein the individual does not show symptoms of frontotemporal dementia.
22. The ~~use method~~ of any one of claims 1-21, wherein the level of PGRN protein in the plasma of the individual after administration of the anti-Sortilin antibody is at least two-fold, three-fold, or four-fold higher than the level of PGRN protein in the plasma of the individual before administration of the anti-Sortilin antibody.
23. The ~~use method~~ of claim 22, wherein the fold increase in the level of PGRN protein in the plasma of the individual is present at about five days after the last administration of the anti-Sortilin antibody.
24. The ~~use method~~ of claim 22 or claim 23, wherein the fold increase in the level of PGRN protein in the plasma of the individual is present at about 28 days, 35 days, 42 days, 49 days, or 56 days after the last administration of the anti-Sortilin antibody.

25. The use method of any one of claims 1-24, wherein the level of PGRN protein in the cerebrospinal fluid of the individual after administration of the anti-Sortilin antibody is at least two-fold higher than the level of PGRN protein in the cerebrospinal fluid of the individual before administration of the anti-Sortilin antibody.
26. The use method of claim 25, wherein the fold increase in the level of PGRN protein in the cerebrospinal fluid of the individual is present at about twelve days after the last administration of the anti-Sortilin antibody.
27. The use method of claim 25 or claim 26, wherein the fold increase in the level of PGRN protein in the cerebrospinal fluid of the individual is present at about 24 days after the last administration of the anti-Sortilin antibody.
28. The use method of any one of claims 25-27, wherein the fold increase in the level of PGRN protein in the cerebrospinal fluid of the individual is present at about 28 days, 35 days, 42 days, 49 days, or 56 days after the last administration of the anti-Sortilin antibody.
29. The use method of any one of claims 1-28, wherein the expression level of SORT1 protein on peripheral white blood cells of the individual after administration of the anti-Sortilin antibody is reduced by at least 50% compared to the expression level of SORT1 protein on peripheral white blood cells of the individual before administration of the anti-Sortilin antibody.
30. The use method of any one of claims 1-29, wherein the expression level of SORT1 protein on peripheral white blood cells of the individual after administration of the anti-Sortilin antibody is reduced by at least 70% compared to the expression level of SORT1 protein on peripheral white blood cells of the individual before administration of the anti-Sortilin antibody.
31. The use method of claim 29 or claim 30, wherein the reduction in the expression level of SORT1 on peripheral white blood cells of the individual is present at about twelve days or more after the last administration of the anti-Sortilin antibody.
32. The use method of claim 29 or claim 30, wherein the reduction in the expression level of SORT1 on peripheral white blood cells of the individual is present at about seventeen days or more after the last administration of the anti-Sortilin antibody.

33. The ~~use method~~ of claim 29 or claim 30, wherein the reduction in the expression level of SORT1 on peripheral white blood cells of the individual is present at about forty days or more after the last administration of the anti-Sortilin antibody.
34. The ~~use method~~ of any one of claims 1-33, wherein the half-life of the anti-Sortilin antibody in plasma is around 5 days.
35. The ~~use method~~ of any one of claims 1-33, wherein the half-life of the anti-Sortilin antibody in plasma is around 8 days.
36. The ~~use method~~ of any one of claims 1-35, wherein the individual is to be treated for a treatment period of up to 48 weeks in length.
37. The ~~use method~~ of any one of claims 1-36, wherein the individual is to be treated for a treatment period of 48 weeks in length.
38. The ~~use method~~ of claim 36 or claim 37, wherein ~~administration of the anti-Sortilin antibody is to be administered~~ occurs on the first day of the treatment period and every four weeks thereafter.
39. The ~~use method~~ of any one of claims 36-38, wherein the anti-Sortilin antibody is to be administered a total of 13 times during the treatment period.
40. The ~~use method~~ of any one of claims 1-39, wherein the disease or injury is frontotemporal dementia (FTD), and wherein plasma neurofilament light chain (NfL) levels are reduced by at least 10% after administration of the anti-Sortilin antibody compared to the plasma neurofilament light chain (NfL) levels before administration of the anti-Sortilin antibody.
41. The ~~use method~~ of any one of claims 1-40, wherein the protein levels of CTSC in the CSF of the individual are increased by at least about 20% after administration of the anti-Sortilin antibody compared to the protein levels of CTSC in the CSF of the individual before administration of the anti-Sortilin antibody.
42. The ~~use method~~ of any one of claims 1-41, wherein the protein levels of SPP1 in the CSF of the individual are decreased by at least about 10% after administration of the anti-Sortilin antibody compared to the protein levels of SPP1 in the CSF of the individual before administration of the anti-Sortilin antibody.

43. The ~~use method~~ of any one of claims 1-42, wherein the protein levels of N-acetylglucosamine kinase (NAGK) in the CSF of the individual are increased after administration of the anti-Sortilin antibody compared to the protein levels of NAGK in the CSF of the individual before administration of the anti-Sortilin antibody.
44. The ~~use method~~ of any one of claims 1-43, wherein the protein levels of one or more inflammatory proteins in the CSF of the individual are decreased after administration of the anti-Sortilin antibody compared to the protein levels of the one or more inflammatory proteins in the CSF of the individual before administration of the anti-Sortilin antibody, wherein the one or more inflammatory proteins are selected from the group consisting of 14-3-3 protein epsilon (YWHAE), allograft inflammatory factor 1 (AIF1), colony stimulating factor 1 (CSF1), chitinase 1 (CHIT1), lymphocyte antigen 86 (LY86), and CD86.
- ~~45. A method of monitoring treatment of an individual being administered an anti-Sortilin antibody, comprising measuring the level of one or more proteins in a sample from the individual before and after the individual has received one or more doses of an anti-Sortilin antibody, wherein the one or more proteins are selected from the group consisting of CTSB, SPP1, NAGK, YWHAE, AIF1, CSF1, CHIT1, LY86, and CD86.~~
- ~~46. The method of claim 45, further comprising assessing the activity of the anti-Sortilin antibody in the individual based on the level of the one or more proteins in the sample.~~
- ~~47. The method of claim 45 or claim 46, wherein the sample is from the cerebrospinal fluid of the individual.~~
- ~~48. The method of claim 46 or claim 47, wherein the anti-Sortilin antibody is determined to be active in the individual if the level of CTSB in the cerebrospinal fluid after the individual has received one or more doses of the anti-Sortilin antibody is increased compared to the level of CTSB in the cerebrospinal fluid before the individual received one or more doses of the anti-Sortilin antibody.~~
- ~~49. The method of claim 48, wherein the anti-Sortilin antibody is determined to be active in the individual if the level of CTSB in the cerebrospinal fluid after the individual has received one or more doses of the anti-Sortilin antibody is increased by at least about 20% compared to the level of CTSB in the cerebrospinal fluid before the individual received one or more doses of the anti-Sortilin antibody.~~

50. ~~The method of any one of claims 46-49, wherein the anti-Sortilin antibody is determined to be active in the individual if the level of SPP1 in the cerebrospinal fluid after the individual has received one or more doses of the anti-Sortilin antibody is decreased compared to the level of SPP1 in the cerebrospinal fluid before the individual has received one or more doses of the anti-Sortilin antibody.~~
51. ~~The method of claim 50, wherein the anti-Sortilin antibody is determined to be active in the individual if the level of SPP1 in the cerebrospinal fluid after the individual has received one or more doses of the anti-Sortilin antibody is decreased by at least about 10% compared to the level of SPP1 in the cerebrospinal fluid before the individual has received one or more doses of the anti-Sortilin antibody.~~
52. ~~The method of any one of claims 46-51, wherein the anti-Sortilin antibody is determined to be active in the individual if the level of NAGK in the cerebrospinal fluid after the individual has received one or more doses of the anti-Sortilin antibody is increased compared to the level of NAGK in the cerebrospinal fluid before the individual has received one or more doses of the anti-Sortilin antibody.~~
53. ~~The method of any one of claims 46-52, wherein the anti-Sortilin antibody is determined to be active in the individual if the levels of one or more inflammatory proteins in the cerebrospinal fluid after the individual has received one or more doses of the anti-Sortilin antibody are decreased compared to the levels of the one or more inflammatory proteins in the cerebrospinal fluid before the individual has received one or more doses of the anti-Sortilin antibody, wherein the one or more inflammatory proteins are selected from the group consisting of 14-3-3 protein epsilon (YWHA ϵ), allograft inflammatory factor 1 (AIF1), colony-stimulating factor 1 (CSF1), chitinase 1 (CHIT1), lymphocyte antigen 86 (LY86), and CD86.~~