

CLAIMS

1. Use of a monoclonal antibody capable of specifically binding to human alpha-synuclein, wherein said antibody binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha-synuclein (SEQ ID NO:10), or
 5 antigen-binding fragment thereof that binds said epitope, in the manufacture of a medicament for treatment together with an additional medicament selected from the group comprising dopamine, caspase inhibitors, calpain inhibitors, LRRK2 inhibitors, BACE1 inhibitors, aggregation inhibitors, antibodies against any form of A β peptides, inflammation inhibitors, LAG-3 antibodies, Isradipine,
 10 molecules reversing alpha-synuclein induced reduction in phagocytic activity of microglia, nicotine, caffeine, modulators of GCase, MAO-B inhibitors, Levodopa/carbidopa, Dopamine agonists, COMT inhibitors and A $_2$ A antagonists wherein said treatment is of Parkinson's disease (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy
 15 Body Disease (DLBD), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy in a subject in need thereof.
2. The use according to claim 1, wherein said medicament is selected from the group comprising pramipexole, VX-765 (Prlnacasan), ABT-957, PF-06447475,
 20 NB-360, Neuropore NPT100-18A, NPT200-11, EGCG, Bapineuzemab, Solanezumab, Gantenerumab, Crenezumab, Aducanumab, C16H15NO $_4$, BMS-986016, GSK2831781, IMP321, ELN484228, NCGC607, Miglustat, Eliglustat (Cerdelga), Azilect, Eldepryl, Zelapar, Pramipexole, Ropinerole, Bromocriptine, Comtess, Tasmar and Istradefyline
- 25 3. The use according to claims 1 or 2, wherein said antibody is capable of competing with an antibody comprising the light chain variable domain of SEQ ID NO:8 and the heavy chain variable domain of SEQ ID NO:7, 30, 31 or 32 for binding to said epitope.
4. The use according to claims 1 or 2, said antibody capable of specifically binding
 30 to an epitope within amino acids 112-115 (SEQ ID NO:19 (ILED)) of

human alpha-synuclein (**SEQ ID NO:10**)), or antigen-binding fragment thereof that binds said epitope.

5. The use according to claims 1, 2 or 4, wherein said antibody is capable of competing with an antibody comprising the heavy chain variable domain of **SEQ ID NO:26** and the light chain variable domain of **SEQ ID NO:27** for binding to said epitope
6. The use according to any one of the preceding claims, the antibody comprising or consisting of an intact antibody selected from the group consisting of antibodies of subtype IgG1, IgG2, IgG3 or IgG4.
7. The use according to any one of the preceding claims, the antibody comprising or consisting of an antigen-binding fragment selected from the group consisting of Fv fragments (e.g. single chain Fv and disulphide-bonded Fv), Fab-like fragments (e.g. Fab fragments, Fab' fragments and F(ab)2 fragments) and domain antibodies (e.g. single VH variable domains or VL variable domains).
8. The use according to any one of the preceding claims, wherein the antibody is a human, humanized, recombinant or chimeric antibody.
9. The use according to any one of the preceding claims 1-3 and 6-8, wherein the antibody or a fragment thereof, comprises:
 - (a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;
 - (b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:2**;
 - (c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;
 - (d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;
 - (e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and
 - (f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.
10. The use according to claim 9, wherein the antibody comprises the heavy chain variable domain of **SEQ ID NO:7** or the light chain variable domain of **SEQ ID NO:8**.

11. The use according to claim 10, wherein the antibody comprises a heavy chain consisting of a variable domain of **SEQ ID NO:7** and a light chain consisting of a variable domain of **SEQ ID NO:8**.
- 5 12. The use according to any one of the preceding claims 1-3 and 6-8, wherein the antibody or a fragment thereof, comprises:
 - (a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;
 - (b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:33**;
 - (c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;
 - 10 (d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;
 - (e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and
 - (f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.
13. The use according to claim 12, wherein the antibody comprises the heavy chain variable domain of **SEQ ID NO:30** or the light chain variable domain of **SEQ ID NO:8**.
- 15 ~~14. The use according to claim 13, wherein the antibody comprises a heavy chain consisting of a variable domain of **SEQ ID NO:30** and a light chain consisting of a variable domain of **SEQ ID NO:8**.~~
- 20 15. The use according to any one of the preceding claims 1-3 and 6-8, wherein the antibody or a fragment thereof, comprises:
 - (a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;
 - (b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:34**;
 - (c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;
 - (d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;
 - 25 (e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and
 - (f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.
16. The use according to claim 15, wherein the antibody comprises the heavy chain variable domain of **SEQ ID NO:31** or the light chain variable domain of **SEQ ID NO:8**.

17. The use according to claim 16, wherein the antibody comprises a heavy chain consisting of a variable domain of **SEQ ID NO:31** and a variable domain of **SEQ ID NO:8**.
- 5 18. The use according to any one of the preceding claims 1-3 and 6-8, wherein the antibody or a fragment thereof, comprises:
- (a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:1**;
 - (b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:35**;
 - (c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:3**;
 - (d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:4**;

10 (e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:5**; and

 - (f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:6**.
19. The use according to claim 18, wherein the antibody comprises the heavy chain variable domain of **SEQ ID NO:32** or the light chain variable domain of **SEQ ID NO:8**.
- 15 20. The use according to claim 19, wherein the antibody comprises a heavy chain consisting of a variable domain of **SEQ ID NO:32** and a variable domain of **SEQ ID NO:8**.
21. The use according to any one of the preceding claims 1-3 and 5-8 wherein the antibody or a fragment thereof, comprises:
- (a) a Heavy Chain CDR1 having the amino acid sequence of **SEQ ID NO:20**;
 - (b) a Heavy Chain CDR2 having the amino acid sequence of **SEQ ID NO:21**;
 - (c) a Heavy Chain CDR3 having the amino acid sequence of **SEQ ID NO:22**;
 - (d) a Light Chain CDR1 having the amino acid sequence of **SEQ ID NO:23**;
 - (e) a Light Chain CDR2 having the amino acid sequence of **SEQ ID NO:24**;

25 and

 - (f) a Light Chain CDR3 having the amino acid sequence of **SEQ ID NO:25**.
22. The use according to claim 21, wherein the antibody comprises a heavy chain variable domain of **SEQ ID NO:26** or the light chain variable domain of **SEQ ID NO:27**.

23. The use according to claim 22, wherein the antibody comprises a heavy chain consisting of a variable domain of **SEQ ID NO:26** and a variable domain of **SEQ ID NO:27**.

24. The use according to any one of the previous claims, comprising a preparation of the monoclonal antibody according to any one of the previous claims, wherein said preparation is substantially free of naturally-arising antibodies that are either not capable of binding to alpha-synuclein or that do not materially alter an anti-alpha-synuclein functionality of the preparation, said functionality being selected from the group consisting of:

- (i) a binding affinity (KD) of the anti-alpha-synuclein antibody for alpha-synuclein;
- (ii) a capability of the anti-alpha-synuclein antibody of inhibiting protease truncation of alpha-synuclein fibrils;
- (iii) a capability of the anti-alpha-synuclein antibody of reversing impairment in basal synaptic transmission in F28-snca transgenic mice;
- (iv) a capability of the anti-alpha-synuclein antibody of reducing levels of alpha-synuclein in the mouse hippocampus as measured by in vivo microdialysis;
- (v) a capability, when administered chronically, of the anti-alpha-synuclein antibody to restore motor function in a rat model of Parkinson's disease
- (vi) a capability to prevent seeding of alpha-synuclein (such as accumulation of insoluble phosphorylated alphasynuclein in vitro and/or in a mouse model of Parkinson's disease); or
- (vii) a capability to bind truncated alpha-synuclein in a human brain.

25. The use according to any one of the previous claims comprising a preparation of the monoclonal antibody according to any one of the previous claims, wherein said monoclonal antibody possesses a structural change in its amino acid sequence, relative to the structure of a naturally-occurring anti-alpha-synuclein antibody, wherein said structural change causes said monoclonal antibody to exhibit an altered functionality relative to the functionality exhibited by said naturally-occurring anti-alpha-synuclein antibody, wherein said functionality being selected from the group consisting of:

- (i) a binding affinity (KD) of the anti-alpha-synuclein monoclonal antibody for alpha-synuclein;
- (ii) a capability of the anti-alpha-synuclein monoclonal antibody of inhibiting protease truncation of alpha-synuclein fibrils;
- 5 (iii) a capability of the anti-alpha-synuclein monoclonal antibody of reversing impairment in basal synaptic transmission in F28-snca transgenic mice;
- (iv) a capability of the anti-alpha-synuclein monoclonal antibody of reducing levels of alpha-synuclein in the mouse hippocampus as measured by in vivo microdialysis;
- 10 (v) a capability, when administered chronically, of the anti-alpha-synuclein monoclonal antibody to restore motor function in a rat model of Parkinson's disease;
- (vi) a capability to prevent seeding of alpha-synuclein (such as accumulation of insoluble phosphorylated alphasynuclein in vitro and/or in a mouse
15 model of Parkinson's disease); or
- (vii) a capability to bind truncated alpha-synuclein in a human brain.

- 26. The use according to claim 1, wherein the treatment is chronic.
- 27. The use according to claim 1, wherein the chronic treatment is for at least 2 weeks.
- 5 28. The use according to claim 1, wherein the subject is human.
- 29. The use or use according to claims 1-28 wherein said monoclonal antibody and additional medicament are to be administered approximately simultaneously or wherein the medicaments are to be taken separately.

30. A kit comprising an antibody as defined in the previous claims and a medicament selected from the group comprising dopamine, caspase inhibitors, calpain inhibitors, LRRK2 inhibitors, BACE inhibitors, aggregation inhibitors, antibodies against A β , inflammation inhibitors, LAG-3 antibodies, Isradipine, molecules reversing alpha-synuclein induced reduction in phagocytic activity of microglia, nicotine, caffeine and modulators of GCase, MAO-B inhibitors, Levodopa/carbidopa, Dopamine agonists, COMT inhibitors and A₂A antagonists
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31. The kit according to claim 31 wherein said medicament is selected from the group comprising pramipexole, VX-765 (Prlnacasan), ABT-957, PF-06447475, NB-360, Neuropore NPT100-18A, NPT200-11, EGCG, Bapineuzumab, Solanezumab, Gantenerumab, Crenezumab, Aducanumab, C16H15NO₄, BMS-986016, GSK2831781, IMP321, ELN484228, NCGC607, Miglustat, Eliglustat (Cerdelga), Azilect, Eldepryl, Zelapar, Pramipexole, Ropinerole, Bromocriptine, Comtess, Tasmar and Istradefylin.
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