

CLAIMS

1. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use in a method of slowing or inhibiting progression of Parkinson's disease (PD) in a subject in need thereof:

5 in which the rAAV comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be introduced into the subject,

in which at least 30% of the volume of the subject's putamen is to be transduced with the GDNF transgene, and

10 in which the subject does not exhibit an increase in PD-associated symptoms for a least 6 months following the introducing as compared to prior to introducing, optionally

in which the rAAV is to be introduced via systemic introduction.

2. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use according to Claim 1, in which the rAAV is to be introduced via local introduction, optionally

15 in which local introduction is introduction directly to the subject's putamen, and/or

in which during the local introduction the rAAV is to be directly introduced to each of the subject's putamen, and/or

in which the local introduction is to be performed simultaneously with non-invasive imaging, optionally

20 in which the non-invasive imaging is selected from the group consisting of intraoperative magnetic resonance image (iMRI)-guided convection enhanced delivery (CED), ultrasound, computed tomography (CT); functional magnetic resonance imaging (fMRI); positron emission tomography (PET); electroencephalography (EEG); magnetoencephalography (MEG); functional near-infrared spectroscopy (fNIRS); and
25 combinations thereof, and/or

in which during the local introduction about half of the rAAV vector is to be introduced to each putamen via intraoperative magnetic resonance image (iMRI)-guided convection enhanced delivery (CED), and/or

in which during local introduction an MRI contrast agent is to be further introduced at substantially the same time as the AAV vector, or

in which the MRI contrast agent is gadoteridol, and/or

in which the MRI contrast agent is to be introduced to the subject in the same composition as the rAAV, or

in which the MRI contrast agent is to be introduced to the subject in a different composition as the rAAV.

3. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use according to Claim 1, in which the rAAV is to be introduced via systemic introduction.

4. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use according to Claim 1, 2 or 3, in which the transduction and/or coverage of the putamen is assessed via Magnetic-resonance imaging, and/or

in which at least 40%, 50%, 60%, 70%, 80%, 90%, 95% or more of the volume of the subject's putamen is to be transduced with the GDNF transgene, and/or

in which the subject does not exhibit a substantial increase in PD-associated symptoms for at least 12 months immediately following the introducing as compared to prior to the introducing, or

in which the subject exhibits a decrease in PD-associated symptoms for at least 6 months or more immediately following the introducing as compared to prior to introducing, or

in which the subject exhibits a decrease in PD-associated symptoms for a least 12 months or more immediately following the introducing as compared to prior to introducing.

5. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use according to Claim 1, in which the subject has an initial Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS) score, prior to introduction, that is less than 32, optionally

in which the slowing or inhibiting the progression of Parkinson's' disease in the subject is characterized by a second MDS-UPDRS score 6 months immediately following the introducing that is not substantially higher than the initial MDS-UPDRS score, and/or

5 in which the slowing or inhibiting the progression of Parkinson's' disease in the subject is characterized by a second MDS-UPDRS score about 12 months immediately following the introducing that is not substantially higher than the initial MDS-UPDRS score, or

in which the subject has an initial MDS-UPDRS score, prior to introduction, that is greater than or equal to 32, optionally

10 in which the subject exhibits a decrease in the initial MDS-UPDRS score for at least 6 months immediately following the introducing as compared to prior to introducing, and/or

15 in which the slowing or inhibiting the progression of Parkinson's' disease in the subject is characterized by a second MDS-UPDRS score about 6 months immediately following the introducing that is at least about 20% lower than the initial MDS-UPDRS score, or

20 in which the slowing or inhibiting the progression of Parkinson's' disease in the subject is characterized by a second MDS-UPDRS score about 12 months immediately following the introducing that is at least about 30% lower than the initial MDS-UPDRS score, or further comprising, prior to introducing, determining an initial MDS-UPDRS score for the subject, or further comprising, prior to introducing, receiving results of an assay that provides an initial MDS-UPDRS score for the subject, or

in which slowing or inhibiting the progression of PD in the subject is characterized by a reduction of an initial MDS-UPDRS score following introduction, optionally

25 in which the reduction is an at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater reduction of the initial MDS-UPDRS score 6 months following introduction, or

in which the reduction is an at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater reduction of the initial MDS-UPDRS score 12 months following introduction, or

30 in which slowing or inhibiting the progression of PD in the subject is characterized stabilization of an initial MDS-UPDRS score following introduction, optionally

in which the stabilization is characterized by no more than a 10% increase or decrease of the initial MDS-UPDRS score, and/or

in which stabilization occurs for at least 6 months or longer, or

in which the subject is mildly affected by PD, optionally

5 in which the subject mildly affected by PD has an initial MDS-UPDRS score less than 32 prior to the introduction of rAAV and was diagnosed with PD less than 5 years prior to the introduction, or further comprising, prior to the introduction, diagnosing the subject as being mildly affected by PD, or further comprising, prior to the introduction, receiving the results of an assay that diagnoses the subject as being mildly affected by PD, or

10 in which the subject is moderately affected by PD, optionally

in which the subject moderately affected by PD has an initial MDS-UPDRS score equal to or greater than 32 prior to the introduction of rAAV and was diagnosed with PD less than 4 years prior to the introduction, or further comprising, prior to the introduction, diagnosing the subject as being moderately affected by PD, or further comprising, prior to introduction, receiving the results of an assay that diagnoses the subject as being moderately affected by PD, or

in which the promoter is a cytomegalovirus (CMV) promoter, or

20 in which the promoter is a nervous system (NS) or central nervous system (CNS) specific promoter, optionally

in which the NS specific promoter is selected from the NS specific promoters in Table 1, or

in which the CNS specific promoter is selected from the CNS specific promoters in Table 2, or

25 in which the GDNF transgene comprises a sequence of SEQ ID NO: 1, or a functional variant that is at least 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% or more identical to SEQ ID NO: 1, or

in which the rAAV is AAV1, AAV2, AAV3, AAV3b, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, Rh10, or a rational haploid thereof, optionally

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in which the rAAV is AAV2, or

in which the rAAV exhibits brain-specific tropism, or

in which the rAAV comprises a modification that increases its brain-specific tropism, optionally

5 in which brain-specific tropism is increased by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater as compared to an unmodified AAV, or

in which the rAAV is to be introduced at a total dose within the range of 5×10^{12} vg to about 1.5×10^{13} vg, optionally

10 in which about one half of the total dose is to be administered to each of the subject's putamen, or

in which the rAAV is to be introduced as a liquid composition comprising the rAAV and a pharmaceutically acceptable carrier, optionally

in which the liquid composition has an rAAV concentration of from about 3×10^{12} vg/mL to about 4×10^{12} vg/mL, or

15 in which at least one anti-PD therapeutic prior to the introduction of the rAAV is to be administered to the subject, or

in which at least one anti-PD therapeutic is to be administered to the subject prior to and following the introduction of the rAAV, and/or

20 in which the at least one anti-PD therapeutic is selected from the group consisting of levodopa, Sinemet, Rytary, Stalevo, amantadine, pramipexole, rotigotine, ropinirole, apomorphine, entacapone, and/or

in which the subject maintains or decreases the dose of the at least one anti-PD therapeutic following introduction, optionally

25 in which the dose of the at least one anti-PD therapeutic is decreased by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or more.

6. A recombinant adeno-associated virus (rAAV) vector comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use in a method of slowing or inhibiting a progression of Parkinson's disease (PD) in a subject in need thereof, the method comprising:

the recombinant adeno-associated virus (rAAV) vector comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be locally introduced to the subject's putamen,

in which at least 30% of the volume of the subject's putamen is to be transduced with the GDNF transgene.

7. A glial cell line-derived neurotrophic factor (GDNF) transgene for use in a method of slowing or inhibiting a progression of PD in a subject in need thereof:

in which greater than or equal to about 30% of the volume of the subject's putamen is to be transduced with the glial cell line-derived neurotrophic factor (GDNF) transgene,

in which the subject does not exhibit a substantial increase in PD-associated symptoms for a least 6 months following the transducing, optionally

in which the transducing is to be performed by administering a rAAV comprising the GDNF transgene to each of the subject's putamen.

8. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter, for use in a method of reducing or stabilizing an initial Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part (MDS-UPDRS) score in a subject having Parkinson's disease (PD):

in which the recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be administered to the subject's putamen,

in which the subject has a second MDS-UPDRS score at 6 months following the administration is decreased or stabilized as compared to the initial MDS-UPDRS score of the subject prior to administering, optionally further comprising the step of, prior to administering, obtaining or receiving an initial MDS-UPDRS score from the subject, or

in which the second MDS-UPDRS score is decreased by at least 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater as compared to the initial MDS-UPDRS score 12 months following administering, or

in which stabilization is no more than a 10% increase or decrease of the initial MDS-UPDRS score.

9. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter, for use in a method of treating a subject mildly affected by Parkinson's disease (PD):

in which the recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be administered to each of the subject's putamen,

in which at least 30% of the subject's putamen is to be transduced with the GDNF transgene, and

in which the subject has a second MDS-UPDRS score at 6 months post-administering that is stabilized as compared to the initial MDS-UPDRS score, optionally

in which the subject has a MDS-UPDRS score at 12 month post-administering that is stabilized as compared to the initial MDS-UPDRS score prior to administering, and/or

in which stabilization is no more than a 10% increase or decrease of the initial MDS-UPDRS score.

10. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter, for use in a method of treating a subject moderately affected by Parkinson's disease (PD):

in which the recombinant adeno-associated virus (AAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be administered to each of the subject's putamen,

in which at least 30% of the subject's putamen is to be transduced with the GDNF transgene, and

in which the subject has a second MDS-UPDRS score at 6 months post-administering that is at least about 20% lower than the initial MDS-UPDRS score, optionally

in which the reduction is an at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or greater as compared to the initial MDS-UPDRS score.

11. A recombinant adeno-associated virus (rAAV) vector comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter, for use in a method of slowing or inhibiting progression of Parkinson's disease (PD) in a subject in need thereof:

in which the recombinant adeno-associated virus (rAAV) vector comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be locally introduced to each of the subject's putamen; and

an MRI contrast agent is to be locally introduced to each of the subject's putamen at substantially the same time as the rAAV,

in which at least 30% of the volume of the subject's putamen is to be transduced with the transgene, and

in which the subject does not exhibit a substantial increase in PD-associated symptoms for a least 6 months immediately following the introducing as compared to prior to introducing, or in which:

the recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter is to be introduced to the subject,

in which at least 30% of the volume of the subject's putamen is to be transduced with the GDNF transgene, and

in which the subject does not exhibit a substantial increase in PD-associated symptoms for a least 6 months immediately following the introducing as compared to prior to introducing.

12. A composition for slowing or inhibiting a progression of Parkinson's disease (PD) in a subject, the composition comprising:

a recombinant adeno-associated virus (rAAV) comprising a genome comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter; and

a pharmaceutically acceptable carrier, optionally

in which the composition has a rAAV concentration of 3×10^{12} vg to 4×10^{12} vg per mL, or

in which the composition comprises an rAAV concentration of 3.3×10^{12} vg per mL.

13. A formulation for slowing or inhibiting a progression of Parkinson's disease (PD) in a subject, the formulation comprising: an adeno-associated virus (AAV) at a concentration of 3×10^{12} vg to 4×10^{12} vg per mL of a pharmaceutically acceptable carrier,

in which the rAAV comprises a genome comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter.

14. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use according to Claim 2, in which the introducing is to be performed at a flow rate of from about 1 μ L/min to about 30 μ L/min.

15. A recombinant adeno-associated virus (rAAV) comprising a glial cell line-derived neurotrophic factor (GDNF) transgene operably linked to a promoter for use according to any of Claims 1 to 6, 8 to 11 and 14, the glial cell line-derived neurotrophic factor (GDNF) transgene for use according to Claim 7, the composition for use according to Claim 12 and the formulation for use according to Claim 13, in which the subject does not exhibit any serious adverse event for at least 6 months immediately following the introducing or administering.