COMPOSITIONS AND METHODS FOR TREATING MULTIPLE SYSTEM ATROPHY (MSA)

FIELD OF THE INVENTION

The present invention relates to clinical uses of antibodies binding to human alpha synuclein for treating synucleinopathies or prodromal synucleinopathy.

REFERENCE TO SEQUENCE LISTING

This application includes one or more Sequence Listings which are disclosed in computer-readable media (file name: "1294-WO-PCT Seq list ST26.xml", created on 21 February 2025, and having a size of 58 KB), which file is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

Synucleinopathies, refer to disorders characterized by the neural inclusion of pathologic alpha synuclein aggregates called Lewy bodies. Synucleinopathies include Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease) and Diffuse Lewy Body (DLB) disease (also known as Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson disease (CAPD), pure autonomic failure (PAF) and multiple system atrophy (MSA; e.g., Olivopontocerebellar Atrophy, Striatonigral Degeneration and Shy-Drager Syndrome).

Alpha synuclein is normally associated with synapses and is believed to play a role in regulating synaptic vesicle release and thereby affecting neural communication, plasticity, learning and memory. States of synucleinopathies have been widely shown to be associated with aggregates of alpha synuclein, however, the precise pathological species of alpha synuclein remains unknown. Various misfolded/aggregated/secreted species ranging from oligomers to fibrils, and different post-translational modifications have been associated with toxicity but there is no consensus on which is most important, if indeed there even is a single toxic species.

The antibodies disclosed in WO2017/009312 bind multiple species of alpha synuclein, including all known major species formed by alternative splicing or posttranslational modifications, such as truncations, as well as oligomeric and fibrillary forms. Such antibodies are believed to be useful in treatment and/or diagnosis of disease involving alpha synuclein, such as synucleinopathies and/or conditions involving abnormal accumulation or deposition

of alpha synuclein in the central nervous system. Methods of generating the antibodies disclosed in WO2017/009312 are also disclosed in that same application, as are various functional and structural characteristics of these antibodies. WO2023/041524 discloses certain dosage regimens for administering the antibodies disclosed in WO2017/009312.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide methods of using anti-alpha synuclein antibodies in the clinic to treat synucleinopathies or prodromal synucleinopathy.

The inventors of the present invention have identified a method of treating MSA in humans using anti-alpha synuclein antibodies. Data presented in the experimental section (Example 8 and Figures 12-20) showed a consistent trend towards the specific anti-alpha synuclein antibody, GM37var2, being capable of slowing clinical progression of disease in MSA patients.

In one aspect the invention provides a monoclonal anti-alpha synuclein antibody for use in the treatment of synucleinopathies or prodromal synucleinopathies, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one aspect the invention provides a monoclonal anti-alpha synuclein antibody for use in the treatment of multiple system atrophy (MSA), wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from MSA or in risk of developing MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In another aspect the invention provides a method of treating synucleinopathies or prodromal synucleinopathies, said method comprises administering a monoclonal anti-alpha

synuclein antibody intravenously to a human subject in need thereof, wherein said human subject is suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In another aspect the invention provides a method of MSA, said method comprises administering a monoclonal anti-alpha synuclein antibody intravenously to a human subject in need thereof, wherein said human subject is suffering from MSA or in risk of developing MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In yet another aspect the invention provides the use of a monoclonal anti-alpha synuclein antibody for the manufacture of a medicament for the treatment of synucleinopathies or prodromal synucleinopathies, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In yet another aspect the invention provides the use of a monoclonal anti-alpha synuclein antibody for the manufacture of a medicament for the treatment of synucleinopathies or prodromal synucleinopathies, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from MSA or in risk of developing MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one embodiment of these aspects the present invention provides suitable clinical uses for treating synucleinopathies, such as Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure or multiple system atrophy (MSA), such as possible MSA, probable MSA, MSA type C, MSA type P, clinically established MSA or clinically probable MSA.

In another embodiment of these aspects the present invention provides suitable clinical uses for treating prodromal synucleinopathies in a human subject in risk of developing synucleinopathy, said human subject being identifiable by exhibiting one or more clinical markers of prodromal synucleinopathies such as REM Sleep Behaviour Disorder (RBD) such as isolated RBD (iRBD), dysfunctional olfaction such as hyposmia, abnormal cognitive performance in neuropsychological testing, subtle motor dysfunction or abnormal motor performance assessed by objective testing, abnormal color vision, autonomic dysfunctions (such as constipation, urinary symptoms, erectile dysfunction, orthostatic hypotension), reduced nigrostriatal dopaminergic binding in the putamen and striatum (abnormal DAT-SPECT), Seborrhoeic dermatitis, or a genotype associated with increasing phenoconversion risk such as mutations in glucocerebrosidase (encoded by the GBA gene).

In particular embodiments the invention provides suitable clinical uses for monoclonal antibody GM37, and its variants; GM37 Variant 1, GM37 Variant 2 and GM37 Variant 3; such antibodies, methods for their manufacture and their characteristics are all disclosed in WO2017/009312.

In particular embodiments of these aspects the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 3-5 weeks, such as about every 4 weeks or once monthly, such as every 28-30 days.

In particular embodiments of these aspects the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of about 750 mg, about 1050 mg, about 1400 mg, about 1750 mg, about 2100 mg, about 2450 mg, about 2800 mg, about 3150 mg, about 3500 mg, about 3850 mg, about 4200 mg, about 4550 mg, about 4900 mg, about 5250 mg, about 5600 mg, about 5950 mg, about 6300 mg, or about 6650 mg. In a further

particular embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of 1050 mg, 2100 mg or 4200 mg.

In one aspect the anti-alpha synuclein antibody is administered in a liquid pharmaceutical composition comprising a full length IgG1 monoclonal anti-alpha synuclein antibody in a concentration of 20-230 mg/mL, such as 25-225 mg/mL, wherein said antibody 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**;

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**;

and wherein the composition further comprises a buffering agent, a pharmaceutically acceptable tonicity agent, a pharmaceutically acceptable surfactant and wherein the pH of the composition is between 4.5 to 7.5, such as 5.0 to 7.0, such as 5.5. to 6.5, such as 6.0.

Other features and advantages of the invention that apply to these aspects and embodiment will be apparent from the following detailed description of the invention, the experimental section and from the claims.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the predicted relationship between doses and CSF exposure and % free alpha synuclein.

Fig. 2 shows the principle of the competition ELISA assay. Following preincubation with increasing concentrations of alpha synuclein (aSN) monomer or fibrils, free IgG is bound by coated aSN monomer and detected with an anti-human IgG (H+L) HRP labelled antibody (Left). Captured IgG levels, reversely proportional with the aSN monomer or fibril concentration, are plotted as relative Luminescence units, and IC50 values are calculated using a four-parameter non-linear fit (Right).

Fig. 3 shows Representative GM37 variant 2 binding curves to monomer (R2 = 0.9895) and fibrillar aSN (R2 = 0.994).

Fig. 4 shows the median (including quartiles) plasma concentration (ng/mL) versus time of GM37 variant 2 for healthy subjects (a) and patients (b) following a single dose of GM37v2 at each dose level.

Fig. 5 shows the dose-normalized GM37 variant 2 plasma concentrations versus time (log-scale) at each dose level.

Fig. 6 shows the free alpha synuclein plasma concentrations versus time for healthy subjects (a) and patients (b) following a single dose of GM37v2 at each dose level.

Fig. 7 shows the free/total alpha synuclein plasma concentrations versus time for healthy subjects (a) and patients (b) following a single dose of GM37v2 at each dose level.

Fig. 8 shows the free/total alpha synuclein plasma concentrations versus individual GM37 variant 2 plasma concentrations.

Fig. 9 shows a competition ELISA measuring binding of four antibodies GM37 wt, GM37 var 1, GM37 var 2 and GM37 var 3 to human alpha synuclein. Plates coated with alpha synuclein are used to detect the amount of antibody remaining after preincubation in solution of each antibody (0.3 µg/mL) with increasing concentration of alpha synuclein (0-1000nM). All four antibodies show similar binding to alpha synuclein.

Fig. 10 compares the effect of anti-alpha synuclein antibodies on phosphorylated alpha synuclein levels in murine primary neurons treated with pathological alpha synuclein fibrillary seeds. Primary neurons were treated with seeds (10 ng) in the presence or absence of four antibodies for use according to the invention GM37, GM37 var 1, GM37 var 2 and GM37 var 3 (2µg). Neurons were fixed and stained after 3 weeks and analysed by Cellomics ARRAYSCAN™ for alpha synuclein phosphoserine 129 positive spots. Cells treated with seeds alone or with seeds plus the isotype control antibody (B12) show significantly increased levels phosphorylation. Cells treated with GM37wt and the 3 variants are able to inhibit phosphorylation of alpha synuclein, they all show the same level of phosphorylation as cells that did not receive seeds. Data is shown as mean ±SD as determined from seven images per well in five wells. N=2.

Fig. 11 shows the CSF concentrations of % free/total alpha synuclein in patients with Parkinson's Disease (PD) by GM37v2 dose at day 3 and day 21 of the study described in example 3 (N=15).

Fig. 12 shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. A 19% slowing of clinical progression in MSA patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the UMSARS Total score.

Fig. 13 shows the clinical effect of GM37v2 in treating MSA. A 22% slowing of clinical progression in MSA patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the UMSARS Part I score.

Fig. 14 shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. A 17% slowing of clinical progression in MSA patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the UMSARS Part II score.

Fig. 15 shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. A 27% slowing of clinical progression in MSA patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the modified UMSARS score.

Figs. 16a and 16b shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. A 50% slowing of clinical progression in MSA-C patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the modified UMSARS score.

Figs. 17a and 17b shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. A 42% slowing of clinical progression in early MSA patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the modified UMSARS score.

Figs. 18a and 18b shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. Improved treatment in the MSA patients treated with GM37var2 was observed compared to placebo when measuring treatment effect with the UMSARS Part IV - Global disability score or the Clinical Global Impression – Severity of Illness score.

Figs. 19a-19c show the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. MRI volumetric analysis showed a smaller regional volumetric reduction in the pons and cerebellar white matter at Week 48 in the MSA patients treated with GM37var2 compared to placebo.

Fig. 20 shows the clinical effect of administration of GM37v2 every 4 weeks in treating MSA. A trend of greater lowering of neurofilament light chain load in CSF was observed in the MSA patients treated with GM37var2 compared to placebo.

DEFINITIONS

The term “full-length antibody” is meant to refer to an antibody format of full length (whole) antibody or substantially full-length. The term particularly refers to an antibody with heavy chains that contain an Fc region. Naturally occurring antibodies typically comprise a tetramer which is usually composed of at least two heavy (H) chains and at least two light (L) chains. Each heavy chain is comprised of a heavy chain variable domain (abbreviated herein as VH) and a heavy chain constant domain, usually comprised of three domains (CH1, CH2 and CH3). Heavy chains can for example be selected from the IgG isotype (IgG1, IgG2, IgG3 and IgG4 subtypes). Each light chain is comprised of a light chain variable domain (abbreviated herein as VL) and a light chain constant domain (CL). Light chains include kappa chains and lambda chains. The VH and VL regions can be further subdivided into regions of hypervariability, termed “complementarity determining regions,” that are interspersed with regions of more conserved sequence, termed “framework regions” (FR). Each VH and VL is composed of three CDR Domains and four FR Domains arranged from amino-terminus to carboxy-terminus in the following order: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4 (or J-region). The variable domains of the heavy and light chains contain a binding domain that interacts with an antigen. In some embodiments the full-length antibody includes antibody variant which can be classified as “Product-related substances” according to the International Conference on Harmonization (ICH) Q6B, Product-related substances are defined as “Molecular variants of the desired product formed during manufacturer and/or storage which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.” Such molecular variants of the antibodies for use according to the invention are meant to include e.g. N-Terminal Modifications such as N-terminal pyroglutamate (pyroGlu), such as truncation, or such as incomplete removal of light chain or heavy chain signal peptides, Asparagine (Asn) deamidation, Aspartate (Asp) isomerization, Succinimide formation, Succinimide hydrolyses, oxidations, cysteine related modifications such as free cysteine (Cys) residues, such as alternative disulfide bond linkage (scrambling), such as trisulfide bonding, such as the formation of thioether, or such as cysteine racemization, Glycosylation, Glycation, C-Terminal Modifications such as removal of C-terminal Lys, such as removal of both C-terminal Lys and Gly, or such as C-terminal amidation.

The term "epitope" means an antigenic determinant capable of specific binding to an antibody. Epitopes usually consist of surface groupings of molecules such as amino acids or

sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and linear epitopes are distinguished in that the binding to the former, but not the latter, is always lost in the presence of denaturing solvents. The epitope may comprise amino acid residues directly involved in the binding and other amino acid residues, which are not directly involved in the binding, such as amino acid residues which are effectively blocked by the specifically antigen-binding peptide (in other words, the amino acid residue is within the footprint of the specifically antigen-binding peptide). The term “112-117 epitope” or “epitope within amino acids 112-117” refers to a region of human alpha synuclein that contains at least 4 of the 6 amino acid residues of 112-117 human alpha synuclein, such as all 6 amino acid residues of 112-117 human alpha synuclein, which epitope does not include any residue from 1-111 (including any residue from 106-111) of human alpha synuclein, nor any residue from 118-140 (including residue 118-120) of human alpha synuclein. As used herein, an antibody for use according to the invention said to bind an “epitope within amino acids 112-117” is capable of specifically binding to human alpha synuclein by binding to at least 4 of the 6 amino acid residues of the 112-117 epitope, such as by binding to the 6 amino acid residues of the 112-117 epitope, without binding any residues from 1-111 (including any residue from 106-111) of human alpha synuclein, nor any residue from 118-140 (including residue 118-120) of human alpha synuclein.

The term "human antibody" (which may be abbreviated to “humAb” or “HuMab”), as used herein, is intended to include antibodies having variable and constant domains derived from human germline immunoglobulin sequences. The human antibodies for use according to the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or during gene rearrangement or by somatic mutation in vivo).

The term “humanized” refer to a molecule, generally prepared using recombinant techniques, having an antigen-binding site derived from an immunoglobulin from a non-human species and a remaining immunoglobulin structure based upon the structure and /or sequence of a human immunoglobulin. The antigen-binding site may comprise either complete non-human antibody variable domains fused to human constant domains, or only the complementarity determining regions (CDRs) of such variable domains grafted to appropriate human framework regions of human variable domains. The framework residues of such humanized molecules may be wild type (e.g., fully human) or they may be modified

to contain one or more amino acid substitutions not found in the human antibody whose sequence has served as the basis for humanization. Another approach focuses not only on providing human-derived constant domains but modifying the variable domains as well so as to reshape them as closely as possible to human form. It is known that the variable domains of both heavy and light chains contain three complementarity-determining regions (CDRs) which vary in response to the antigens in question and determine binding capability, flanked by four framework regions (FRs) which are relatively conserved in a given species and which putatively provide a scaffolding for the CDRs. When nonhuman antibodies are prepared with respect to a particular antigen, the variable domains can be "reshaped" or "humanized" by grafting CDRs derived from nonhuman antibody on the FRs present in the human antibody to be modified.

In the present context, "treatment" or "treating" is intended to indicate the clinically relevant management and care of a patient for the purpose of alleviating, arresting, partly arresting, removing, delaying or slowing progression of one or more of the clinical manifestations of the disease. For purposes of this invention, "treatment" or "treating" further means an approach for obtaining beneficial or desired clinical results, where "beneficial or desired clinical results" include, without limitation, alleviation of a symptom, diminishment of the extent of a disorder or disease, stabilized (i.e., not worsening) disease or disorder state, delay or slowing of the progression a disease or disorder state, amelioration or palliation of a disease or disorder state, or remission of a disease or disorder, whether partial or total. In a particular embodiment the "treatment" or "treatment effect" consists of delaying or slowing disease progression in a patient suffering from synucleinopathy, in a particular embodiment this synucleinopathy is MSA, such MSA may be selected from one or more of the MSA subtypes, such as clinically established MSA, clinically probable MSA, possible MSA, probable MSA, MSA type C or MSA type P. In another embodiment "treatment" means to delay the disease onset in a patient with prodromal synucleinopathy. The treatment can be measured by quantifying clinical efficacy or treatment effect by measuring slowing or delay in disease progression, as assessed by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I and Part II Total score (UMSARS TS) or in the modified UMSARS Part I (mUMSARS) or in the abbreviated UMSARS (aUMSARS) up to End-of-Treatment (EoT), i.e. at the end of the treatment period of 24 weeks, 48 weeks, 72 weeks, 96 weeks or more. The treatment can also be measured by quantifying clinical efficacy or treatment effect by measuring slowing or delay in disease progression, as assessed by

longitudinal changes from baseline in the UMSARS Part I, modified UMSARS Part I (mUMSARS) and/or UMSARS Part II scores up to EoT. Such disease progression could also be assessed as the change from baseline up to EoT in UMSARS TS, UMSARS Part I, mUMSARS and/or UMSARS Part II scores. The disease progression can also be assessed by longitudinal changes from baseline in the abbreviated UMSARS (aUMSARS) up to EoT or as change from baseline in Brain Volume, as Measured by Volumetric MRI (vMRI) or as change from baseline in Neurofilament Light Chain (NfL) blood concentrations. The treatment can also be measured by quantifying clinical efficacy or treatment effect by measuring slowing or delay in disease progression, as assessed by longitudinal changes from baseline in one or more parameter selected from: Schwab and England Activities of Daily Living (SE-ADL) Score; as change from baseline in Clinical Global Impression – Severity of Illness (CGI-S) Score; as change from baseline in Patient Global Impression – Severity of Illness (PGI-S) Score; as change from baseline in Observer-Reported Global Impression – Severity of Illness (OGI-S) Score; as change from baseline in Composite Autonomic Symptom Score Select Change (COMPASS Select Change) Score; as change from baseline in UMSARS Part IV Score; as change from baseline in Speech, Swallowing, Falls, and Walking, as assessed by the UMSARS Part I Item Scores; as change from baseline in Frequency, Cause, and Consequence of Falls, as assessed by the Fall Diary Periods; as change from baseline in EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Score; as change from baseline in Brain Volume, as Measured by Volumetric MRI (vMRI); as change from baseline in Tissue Integrity, as Measured by Diffusion-Tensor Imaging (DTI) MRI; as change from baseline in Neurofilament Light Chain (NfL) blood concentrations; as change from baseline in heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III; as change from baseline in gait parameters or frequency of falls, as assessed by digital wearable sensor-based devices that are capable of tracking relevant gait parameters and/or registering falls; as change from baseline in cerebral blood flow, as measured by arterial spin labelling (ASL) MRI; as change from baseline in t-tau and NfL CSF concentrations; or as change from baseline in pathological species of α-synuclein in CSF. The patient to be treated can be identified or diagnosed via any acknowledged method or criteria in the relevant field.

The term "kd" (sec^{-1} or 1/s), as used herein, refers to the dissociation rate constant of a particular antibody-antigen interaction. Said value is also referred to as the koff value.

The term "ka" (M^{-1} x sec^{-1} or 1/Msec), as used herein, refers to the association rate constant of a particular antibody-antigen interaction.

The term "KD" (M), as used herein, refers to the dissociation equilibrium constant of a particular antibody-antigen interaction and is obtained by dividing the kd by the ka. KD may be determined by methods, as described in example 6A, or other methods known in the art.

The term "KA" (M^{-1} or 1/M), as used herein, refers to the association equilibrium constant of a particular antibody-antigen interaction and is obtained by dividing the ka by the kd.

The term “IC50”, as used herein, refers to the antibody concentration at which 50% of the maximum inhibitory effect is reached. The exact IC50 value, usually in nM is depending on the specific assay and therefore not directly comparable between different assays.

The term “Emax”, as used herein, refers to the maximal effect of the antibody at high antibody concentrations, i.e. when all alpha synuclein is bound by the antibody.

The term “avidity”, as used herein, refers to the accumulated strength of an antibody-antigen complex. Here this covers two affinities of individual non-covalent binding interactions between an IgG molecule and its antigen.

The term ”Cmax” as used herein, refers to the maximal concentration of an antibody as measured in plasma of a subject following infusion of said antibody.

The term ”tmax” as used herein, refers to the time it takes to reach Cmax following infusion of an antibody.

The phrase “use according to the invention” as used throughout this disclosure is meant to apply to all uses and methods, including use in the treatment of synucleinopathies or prodromal synucleinopathies, methods of treating synucleinopathies or prodromal synucleinopathies, and use of a monoclonal anti-alpha synuclein antibody for the manufacture of a medicament for the treatment of synucleinopathies or prodromal synucleinopathies. Such use may include administering the monoclonal anti-alpha synuclein antibody, such as GM37v2, to a patient in need thereof using suitable doses, dosing regimens and/or in a suitable pharmaceutical formulation. Such formulations or compositions are also provided by the present invention.

The terms “formulation” and “composition” are used interchangeably throughout this application.

The term “stable compositions” are meant to refer to a composition which can be stored for a specific amount of time, here at least 6 months or more, at specific conditions, here at normal storage conditions for antibody formulations, such as storage at about 5°C, wherein the protein in the composition essentially retains its physical stability and/or chemical stability and/or biological activity. Various analytical techniques for measuring protein

stability are available and well known in the art, some of these are also described in the experimental section herein. Stability can be measured at a selected temperature for a selected time period. In certain embodiments, the formulation is stable at about 40°C for at least about 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, or more days. In certain embodiments, the formulation is stable at about 40°C ± 3°C for at least about 1, 2, 3, 4, 5, 6, 7, 8, or more weeks. In certain embodiments, the formulation is stable at about 25°C for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or more months. In certain embodiments, the formulation is stable at about 5°C ± 3°C for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or more months. In certain embodiments, the formulation is stable at about -20°C ± 3°C for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. Furthermore, the formulation is preferably stable following freezing (to, e.g., -20°C, -40°C or -70°C) and thawing of the formulation, for example following 1, 2 3, 4, or 5 cycles of freezing and thawing. Stability can be evaluated qualitatively and/or quantitatively in a variety of different ways, including evaluation of aggregate formation (for example using size exclusion chromatography, by measuring turbidity, and/or by visual inspection); by assessing charge heterogeneity using cation exchange chromatography, image capillary isoelectric focusing (icIEF) or capillary zone electrophoresis; amino-terminal or carboxy-terminal sequence analysis; mass spectrometric analysis; SDS-PAGE analysis to compare reduced and intact antibody; peptide map (for example tryptic or LYS-C) analysis; evaluating biological activity or antigen binding function of the antibody; etc. Instability may involve any one or more of: aggregation, deamidation (e.g. Asn deamidation), oxidation (e.g. Met oxidation), isomerization (e.g. Asp isomerization), clipping/hydrolysis/fragmentation (e.g. hinge region fragmentation), succinimide formation, unpaired cysteine(s), N-terminal extension, C-terminal processing, glycosylation differences, etc.

A “low viscosity composition” is meant to describe a liquid pharmaceutical composition having a viscosity at least below about 20 cP, such as below 15 cP, such as below 14 cP, such as below 13 cP, such as below 12 cP, such as below 11 cP, such as below 10 cP, such as below 9 cP, such as below 8 cP, such as below 7 cP, such as below 6 cP, such as below 5 cP.

In the present application a “buffering agent” refers to a buffered solution that resists changes in pH by the action of its acid-base conjugate components. The buffers or buffering agents (used interchangeably) of this invention preferably maintains a pH of the composition

in the range from about 4.5 to about 7.5, such as from about 5.5 to about 6.5, for example from 5.7 to 6.4, 5.8 to 6.3 or 5.9 to 6.2. In one embodiment the buffer has a pH of 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5 or 7.0. Histidine buffers (such as L-histidine) are example of buffers that will control the pH in this range. Examples of buffering agents are Acetate, Citrate, Tartrate, Histidine (such as L-Histidine), Glutamate, Phosphate, Tris, Glycine, Bicarbonate, Succinate, Sulfate and Nitrate buffers or a mixture thereof. In some embodiments the buffering agent is selected from sodium phosphate, histidine (such as L-histidine), citric acid, sodium citrate, sodium acetate or a mixture thereof. In one specific embodiment, the buffering agent is a Histidine buffer (such as L-Histidine) or a mixture of Histidine buffers.

In the present application “surfactant” refers to a surface-active agent, preferably a non-ionic surfactant. Examples of surfactants herein include polysorbate (for example, polysorbate 20 and, polysorbate 80); poloxamer (e.g. poloxamer 188); Triton; Triton X-100; sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g. lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyldimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol. In one specific embodiment, the pharmaceutically acceptable surfactant is polysorbate 80 also known as Tween 80.

In the present application “tonicity agent” refers to an excipient which enables an isotonic liquid pharmaceutical composition. Isotonic means that the formulation of interest has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm. Examples of tonicity agents include Mannitol, Sorbitol, Lactose, Dextrose, Trehalose, Sodium Chloride, Potassium Chloride, Glycerol and Glycerine. In one specific embodiment, the tonicity agent is a suitable salt such as NaCl.

In the present context a “bulking agent” is meant to refer to an excipient which provides additional stability to the liquid pharmaceutical composition. Examples of bulking agent include these main classes of excipients: Sugars and polyols (such as Sucrose, Trehalose, Glucose, Lactose, Sorbitol, Mannitol and Glycerol); Amino Acids (such as Arginine, Aspartic

Acid, Glutamic acid, Lysine, Glycine, Glutamate, Histidine, Methionine or Alanine); and Polymers and proteins (such as Gelatin, PVP, PLGA, PEG, dextran, cyclodextrin and derivatives, starch derivatives, HSA or BSA). In one specific embodiment, the bulking agent is sucrose.

The term "Histidine buffer" or "Histidine" is meant to cover Histidine buffers and mixtures thereof such as Histidine, L-Histidine, L-Histidine hydrochloride, L-Histidine monohydrochloride, L-Histidine monohydrate and L-Histidine hydrochloride monohydrate or mixtures thereof. In one specific embodiment, the histidine buffer is a mixture of L-Histidine and L-Histidine monohydrochloride.

The term "about", as used herein, refers to ±10% of a specified value.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to suitable clinical uses of monoclonal antibodies directed to human alpha synuclein for use in the treatment of synucleinopathies or prodromal synucleinopathies.

The inventors of the present invention have identified a method of treating MSA in humans using anti-alpha synuclein antibodies. Data presented in the experimental section (Example 8 and Figures 12-20) showed a consistent trend towards the specific anti-alpha synuclein antibody, GM37var2 (Amlenetug), being capable of slowing clinical progression of disease in MSA patients. Results further showed a slowing in both functional and motor deterioration in participants with early MSA treated with GM37v2 (Amlenetug), as measured by UMSARS total and sub-scores, reaching up to 27% slowing when the mUMSARS score was used to measure treatment effect.

In addition, a subgroups analysis showed that even greater treatment effects were observed in MSA patients diagnosed with MSA-C and/or early MSA as identified by having a low baseline UMSARS total score, e.g. an UMSARS baseline TS of below 40.

The treatment effects observed when measuring effect on the UMSARS scales were also corroborated by trends of efficacy in other clinically relevant measures of global disease severity and function. The volumetric MRI analysis of pons and cerebellar white matter showed a slowing of white matter volume loss in the group exposed to GM37var2 (Amlenetug).

Collectively the data presented herein, provide evidence of a clinical benefit from treatment of MSA patients with GM37var2 (Amlenetug), and surprisingly the treatment effect was most profound in MSA patients with early MSA and/or diagnosed with MSA-C.

In one aspect the invention provides a monoclonal anti-alpha synuclein antibody for use in the treatment of synucleinopathies or prodromal synucleinopathies, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one aspect the invention provides a monoclonal anti-alpha synuclein antibody for use in the treatment of MSA, wherein said use comprises administering said anti-alpha synuclein antibody to a human subject suffering from MSA.

In one aspect the invention provides a monoclonal anti-alpha synuclein antibody for use in the treatment of MSA, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from MSA or in risk of developing MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In another aspect the invention provides a method of treating synucleinopathies or prodromal synucleinopathies, said method comprises administering a monoclonal anti-alpha synuclein antibody intravenously to a human subject in need thereof, wherein said human subject is suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In another aspect the invention provides a method of treating MSA, said method comprises administering a monoclonal anti-alpha synuclein antibody to a human subject in need thereof, wherein said human subject is suffering from MSA.

In another aspect the invention provides a method of treating MSA, said method comprises administering a monoclonal anti-alpha synuclein antibody intravenously to a human subject in need thereof, wherein said human subject is suffering from MSA or in risk of developing MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In yet another aspect the invention provides the use of a monoclonal anti-alpha synuclein antibody for the manufacture of a medicament for the treatment of synucleinopathies or prodromal synucleinopathies, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg and wherein said monoclonal anti-alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In yet another aspect the invention provides the use of a monoclonal anti-alpha synuclein antibody for the manufacture of a medicament for the treatment of MSA, wherein said use comprises administering said anti-alpha synuclein antibody to a human subject suffering from MSA.

In yet another aspect the invention provides the use of a monoclonal anti-alpha synuclein antibody for the manufacture of a medicament for the treatment of MSA, wherein said use comprises administering said anti-alpha synuclein antibody intravenously to a human subject suffering from MSA or in risk of developing MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg and wherein said monoclonal anti-alpha synuclein

antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In certain embodiments the monoclonal anti-alpha synuclein antibody has an estimated KD value of binding to the oligomeric form of alpha synuclein of about 0.1-1.0 nM, such as 0.2-0.8 nM, such as 0.4-0.6 nM, such as about 0.5 nM.

In certain embodiments the monoclonal anti-alpha synuclein antibody has a KD value of binding to the monomeric form of alpha synuclein of about 30-40 nM, such as 32-38 nM, such as 34-37 nM, such as about 36 nM, and an estimated KD value of binding to the oligomeric form of alpha synuclein of about 0.1-1.0 nM, such as 0.2-0.8 nM, such as 0.4-0.6 nM, such as about 0.5 nM. In one embodiment, the ratio between the monomeric and oligomeric binding values is approximately 60-70 fold enhanced to the oligomeric form as compared to the monomeric form, such as 62-68 fold enhancement, such as 64-66 fold enhancement, such as 65 fold enhancement, such enhancement in binding between the two forms is further explained in the experimental section and denoted “avidity gain”. Such enhancement of binding between the two forms will be denoted avidity-gain in this disclosure. In certain embodiments the monoclonal anti-alpha synuclein antibody has a human T½ of about 25-35 days, such as about 4 weeks, such as about 27-33 days, such as about 28 days, such as about 28-32 days, such as 30 days, such as 28-30 days.

In an embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention 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**.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention 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**.

In an embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention 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**;
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**.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention 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**.

In an embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention 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**;
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**.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention comprises a heavy chain variable domain consisting of **SEQ ID NO:31** and a light chain variable domain consisting of **SEQ ID NO:8**.

In an embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention 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**;
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**.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention comprises a heavy chain consisting of a variable domain of **SEQ ID NO:32** and a light chain consisting of a variable domain of **SEQ ID NO:8**.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is a full-length human antibody. In such embodiment the monoclonal anti-alpha synuclein antibody can e.g. be a human IgG1 antibody.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention comprises a human IgG1 heavy chain constant region and/or a human kappa light chain constant region.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention comprises a constant heavy chain domain as defined in **SEQ ID NO:18** and/or a kappa light chain constant domain as defined in **SEQ ID NO:17**.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is antibody GM37, or its variants; GM37 Variant 1, GM37 Variant 2 or GM37 Variant 3. In a preferred embodiment the antibody is GM37v2 (Amlenetug). In a preferred embodiment the antibody is Amlenetug.

In one embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 1000 mg to 4500 mg, or such as between 2000 mg to 4300 mg. In a specific embodiment the monoclonal anti-alpha synuclein antibody is administered at an interval of 3-5 weeks, or said antibody is administered to the human subject in another regime that provides substantially the same area under the curve (AUC) for the exposure of said antibody, or substantially the same estimated target engagement of oligomeric alpha synuclein in CSF of the patient.

In some embodiments the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 6 weeks, every 5 weeks, every 4 weeks, every 3 weeks, every 2 weeks, or every week. In some embodiments the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 20 days, every 21 days, every 22 days, every 23 days, every 24 days, every 25 days, every 26 days, every 27 days, every 28 days, every 29 days, every 30 days, every 31 days, every 32 days, every 33 days, every 34 days, every 35 days, every 36 days, every 37 days, every 38 days, every 39 days, or every 40 days.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 3-5 weeks, such as every 4 weeks or once monthly, such as every 25-31 days, such as every 28-30 days.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of about 75 mg, about 225 mg, about 750 mg, about 2250 mg, about 4500 mg or about 9000 mg.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of 4000 mg to 7000 mg, such as between 4000 mg to 6500 mg, or between 4200 mg to 6300 mg, such as 4200 mg or such as 6300 mg.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of about 750 mg, about 1050 mg, about 1400 mg, about 1750 mg, about 2100 mg, about 2450 mg, about 2800 mg, about 3150 mg, about 3500 mg, about 3850 mg, about 4200 mg, about 4550 mg, about 4900 mg, about 5250 mg, about 5600 mg, about 5950 mg, about 6300 mg, or about 6650 mg. In a further particular embodiment, the monoclonal anti-alpha synuclein antibody for use according to the

invention is administered at a dose of about 1050 mg, about 2100 mg, about 4200 mg or about 6300 mg.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose as specified above by intravenous infusion over 30 minutes ±10 minutes, such as over 20 minutes, 25 minutes, 30 minutes, 35 minutes or 40 minutes.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose as specified above by intravenous infusion over 15 minutes ±5 minutes, such as over 10 minutes, 15 minutes or 20 minutes.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose as specified above by intravenous infusion a speed of about 30 mg/min to about 150 mg/min, such as about 35 mg/min, about 70 mg/min or about 140 mg/min.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose as specified above by intravenous infusion a speed of about 25 mg/min to about 300 mg/min, such as 60 mg/min to about 300 mg/min, such as about 70 mg/min, about 140 mg/min or about 280 mg/min.

In an embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered in an amount and a frequency sufficient to achieve an estimated CSF mean steady state concentration of said antibody of at least 0.5 nM, such as at least 1 nM, such as at least 2 nM, such as at least 3 nM, such as at least 4 nM, such as at least 5 nM, such as at least 6 nM, such as at least 7 nM, such as at least 8 nM, such as at least 9 nM, such as at least 10 nM, such as at least 11 nM, such as at least 12 nM, such as at least 13 nM, such as at least 14 nM, or such as at least 15 nM.

In another embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 50 %, such as at least 55 %, such as at least 60 %, such as at least 75 %, such as at least 77 %, such as at least 80 %, such as at least 82 %, such as at least 85 %, such as at least 87 %, such as at least 90 %, such as at least 92%, such as at least 95 %, such as at least 97% or such as at least 99 %.

In another embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention, is for use in the treatment of synucleinopathies. Such synucleinopathies may be selected from the group comprising: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA). Such treatment may consist of slowing or delaying disease progression of the synucleinopathy (such as the MSA progression) or delaying disease onset if the patient has prodromal synucleinopathy.

In a particular embodiment the synucleinopathy to be treated is Parkinson's disease (PD).

In yet another particular embodiment the synucleinopathy to be treated is Dementia with Lewy Bodies (DLB).

In yet another particular embodiment, the synucleinopathy to be treated is multiple system atrophy (MSA). In such embodiment the human subject suffering from MSA has multiple system atrophy parkinsonian type (MSA-P) or multiple system atrophy cerebellar type (MSA-C) subtype or having been diagnosed with possible or probable MSA, such possible or probable MSA may also be of the multiple system atrophy parkinsonian type (MSA-P) or multiple system atrophy cerebellar type (MSA-C) subtype or having been diagnosed with clinically established MSA or clinically probable MSA, which may also be of the multiple system atrophy parkinsonian type (MSA-P) or multiple system atrophy cerebellar type (MSA-C) subtype.

In yet another embodiment the MSA diagnosis is based on the presence of one or more suitable biomarkers for MSA identified in said human subject. Such biomarkers may be selected from the group comprising: physiologic biomarkers, biologic biomarkers, genetic biomarkers, molecular biomarkers, histologic biomarkers, radiographic biomarkers, imaging biomarkers, behavioral biomarkers or digital biomarkers. In further such embodiment the human subject suffering from MSA or having been diagnosed with possible or probable multiple system atrophy (MSA) or other MSA subtypes may be identifiable by validated clinical assesment and/or diagnostic methods which are known in the art. In another such embodiment, the human subject suffering from MSA or having been diagnosed with possible or probable multiple system atrophy (MSA) or other MSA subtypes may be identifiable by

having had onset of motor and/or autonomic (orthostatic or urinary) MSA symptoms within the last 5 years, such as within the last 4 years, or such as within the last 3 years, or such as within the last 2 years, such as within the last year or such as within the last 6 months.

In yet another such embodiment, the human subject suffering from MSA or having been diagnosed with possible or probable multiple system atrophy (MSA) or other MSA subtypes may be identifiable by having an UMSARS Part I score ≤16 (when omitting item 11 on sexual function). In yet another such embodiment the human subject suffering from MSA or having been diagnosed with possible or probable multiple system atrophy (MSA) or other MSA subtypes may be identifiable by having a cognitive performance evaluated by the Montreal Cognitive Assessment (MoCA) with a score ≥22.

In yet another such embodiment, the human subject suffering from MSA has MSA-C. In yet another such embodiment, the human subject suffering from MSA has MSA-P. In yet another such embodiment, the human subject suffering from MSA has possible or probable MSA-C. In yet another such embodiment, the human subject suffering from MSA has possible or probable MSA-P. In yet another such embodiment, the human subject suffering from MSA has clinically established or clinically probable MSA. In yet another such embodiment, the human subject suffering from MSA has clinically established or clinically probable MSA-P. In yet another such embodiment, the human subject suffering from MSA has clinically established or clinically probable MSA-C.

In yet another such embodiment, the human subject suffering from MSA has MSA in the early disease stage. In yet another such embodiment, the human subject suffering from MSA has MSA in an early disease stage. In yet another such embodiment, the human subject suffering from MSA has MSA in a disease stage where said patient is not yet majorly impaired by the disease, such as e.g. having an UMSARS TS of below 40 (e.g., 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15). In yet another such embodiment, the human subject suffering from MSA has early MSA. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34,

below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody.

In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15. In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody.

In another embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention, is for use in the treatment of prodromal synucleinopathies in a human subject in risk of developing synucleinopathy, said human subject being identifiable by exhibiting one or more clinical markers of prodromal synucleinopathies selected from the group comprising: REM Sleep Behaviour Disorder (RBD) such as isolated RBD (iRBD), dysfunctional olfaction such as hyposmia, abnormal cognitive performance in neuropsychological testing, subtle motor dysfunction or abnormal motor performance assessed by objective testing, abnormal color vision, autonomic dysfunctions (such as constipation, urinary symptoms, erectile dysfunction, orthostatic hypotension), reduced nigrostriatal dopaminergic binding in the putamen and striatum (abnormal DAT-SPECT), and a genotype associated with increasing phenoconversion risk such as mutations in glucocerebrosidase (encoded by the GBA gene). In such embodiment the human subject in risk of developing synucleinopathy, may be identifiable by exhibiting RBD such as isolated RBD (iRBD), and at least one additional clinical marker of prodromal synucleinopathies, such as hyposmia and/or abnormal DAT-SPECT. In yet another such embodiment the human subject in risk of developing synucleinopathy, may be identifiable by exhibiting RBD, such as isolated RBD (iRBD), and hyposmia and abnormal DAT-SPECT.

In an aspect the monoclonal anti-alpha synuclein antibody, such as GM37v2, is formulated in one of the specific liquid pharmaceutical compositions as provided in the present application.

In another aspect is provided a kit comprising the monoclonal anti-alpha synuclein antibody for use according to the invention.

In yet another embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention, is expressed in or obtained by expression in CHO cells.

In an aspect the monoclonal anti-alpha synuclein antibody for use according to the invention, is for use in treating abnormal aggregation of alpha synuclein in a human subject, wherein said human subject has been identified as having abnormal aggregation of alpha synuclein in CNS.

In some embodiments of the treatment with the monoclonal anti-alpha synuclein antibody for use according to the invention can continue for weeks, months, a year, or even several years. In further embodiments the treatment can be part of a combination therapy in which the monoclonal antibody for use according to the invention is given in combination with or adjunctive to one or more additional pharmaceutical agents. Such additional pharmaceutical agents may be part of the standard of care utilized in the specific synucleinopathy. In MSA such standard of care may for example include one or more of the following medicaments: medications to reduce Parkinson's disease-like signs and symptoms, such as levodopa and/or carbidopa, or medicaments know to be useful in treating autonomic symptoms (such as urinary symptoms or neurogenetic orthostatic hypotension), such medicaments may be selected from pyridostigmine, midodrine or droxidopa.

Specific doses and Dosage regimens

Doses and dosage regimens may be expressed in fixed doses such as a specific amount of mg of a monoclonal antibody for use according to the invention (i.e., independent of the body weight of the human subject to be treated). Such doses are described in the embodiments and aspects of the present invention including Table 1 below. In some embodiments, doses or dosage regimens may also be expressed in mg/kg (i.e., a dose which varies based on the body weight of the human subject to be treated). It will be within the skills of a trained physician to convert between fixed doses and doses administered according to body weight (such as mg/kg). The result of the conversion will depend on the body weight of the human subject to be treated with doses or dosage regimens.

In one embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of between 1000 mg to 4500 mg at an interval of 3-5

weeks, or said antibody is administered to the human subject in another regime that provides substantially the same estimated target engagement of oligomeric alpha synuclein in CSF of the patient. In a particular embodiment said antibody is administered to the human subject in a regime that provides substantially the same estimated target engagement of oligomeric alpha synuclein in CSF of the patient as 4200 mg GM37v2 dosed about every 4 weeks.

In some embodiments the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 4 weeks. In some embodiments the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every month. In some embodiments the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 27 days, every 28 days, every 29 days, every 30 days, or every 31 days.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered every 3-5 weeks, such as every 4 weeks or once monthly, such as every 28-30 days.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of 1000 mg to 4500 mg, such as between 2000 mg to 4500 mg, or between 3500 mg to 4500 mg, such as 4200 mg.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of about 1050 mg, about 1400 mg, about 1750 mg, about 2100 mg, about 2450 mg, about 2800 mg, about 3150 mg, about 3500 mg, about 3850 mg, about 4200 mg. In a further particular embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of 1050 mg, 2100 mg or 4200 mg.

In one embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of between 13 mg/kg to 71 mg/kg, or such as between 14 mg/kg to 64 mg/kg, or such as between 15 mg/kg to 60 mg/kg, or such as 15 mg/kg, or such as 30 mg/kg, or such as 60 mg/kg at an interval of 3-5 weeks, or said antibody is administered to the human subject in another regime that provides substantially the same estimated target engagement of oligomeric alpha synuclein in CSF of the patient. In a particular

embodiment said antibody is administered to the human subject in a regime that provides substantially the same estimated target engagement of oligomeric alpha synuclein in CSF of the patient as 60 mg/kg GM37v2 dosed about every 4 weeks.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of about 1 mg/kg, about 3 mg/kg, about 11 mg/kg, about 32 mg/kg, about 64 mg/kg or about 129 mg/kg.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of 14 mg/kg to 64 mg/kg, such as between 15 mg/kg to 60, such as between 30 mg/kg to 60 mg/kg, such as 60 mg/kg.

In a particular embodiment the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of about 11 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, or about 95 mg/kg. In a further particular embodiment, the monoclonal anti-alpha synuclein antibody for use according to the invention is administered at a dose of 15 mg/kg, 30 mg/kg or 60 mg/kg.

In a particular embodiment the patient to be treated has a body weight of between 50 to 110 kg, such as 50 kg, 55 kg, 60 kg, 65 kg, 70 kg, 75 kg, 80 kg, 85 kg, 90 kg, 95 kg, 100 kg, 105 kg or 110 kg. In the clinical study disclosed in Example 3 the average body weight of the human subjects included were about 70 kg.

In some embodiments the doses and dosage regimens of the present invention may also be expressed as the amount and the administration frequency of a monoclonal antibody, such as GM37v2, which provides sufficient estimated CSF mean steady state concentration, sufficient AUC exposure or sufficient estimated target engagement to oligomeric forms of alpha synuclein in CSF to obtain clinical efficacy.

The table below specify the conversion between the relevant dosage formats for an illustrative human subject with a body weight of 70 kg.

Table 1: Doses and conversion between dosage formats and estimates of target engagement in CSF and mean steady state concentrations in CSF with IV dosing intervals of about 28 days.

Dose per kg body weight (mg/kg)	Fixed dose for patient with 70 kg body weight (mg)	Estimated CSF mean steady state concentration (nM)	Estimated target engagement to oligomeric forms of alpha synuclein in CSF (%)
10	700	*	*
15	1050	3	85
20	1400	*	*
25	1750	*	*
30	2100	6	90
35	2450	*	*
40	2800	*	*
45	3150	*	*
50	3500	*	*
55	3850	*	*
60	4200	12	95
65	4550	*	*
70	4900	*	*
75	5250	*	*
80	5600	*	*
85	5950	*	*
90	6300	18	97
95	6650	*	*
100	7000	*	*
110	7700	*	*
120	8400	*	*

130	9100	*	*

* for each dose the estimated CSF mean Css and target engagement in CSF for aggregated/oligomeric alpha synuclein can be calculated as described in example 1.

Exemplary dosing regimens are provided in the table below:

Route and frequency	**Dose**
IV infusion, about every 4 weeks (or monthly)	1050 mg or 15 mg/kg
IV infusion, about every 4 weeks (or monthly)	2100 mg or 30 mg/kg
IV infusion, about every 4 weeks (or monthly)	4200 mg or 60 mg/kg
IV infusion, about every 4 weeks (or monthly)	6300 mg or 90 mg/kg

For the purpose of this disclosure the CSF concentrations of antibodies for use according to the invention and the brain interstitial fluid (ISF) concentrations of said antibodies are assumed to be equal.

In one embodiment, GM37v2 is administered intravenously and dosed such that a desired therapeutic concentration is achieved in CSF and/or ISF of the human subject. In one embodiment, the antibody achieves a concentration sufficient to enter the brain and produce a therapeutic effect, e.g., mediated by binding to aggregated alpha synuclein and triggering microglia-dependent and/or independent clearance/inactivation, and/or reducing a-synuclein aggregation, and/or preventing prion-like intracellular spread of a-synuclein.

In another embodiment, the desired therapeutic concentration of GM37v2 in CSF and/or ISF can be equal to the concentration that is able to provide and maintain (after 1 or more doses) at least 10-100%, such as 20-90%, such as 30-80% such as 40-70%, such as 50-60%, such as at least 10%, such as at least 20%, such as at least 30%, such as at least 40%, such as at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 95% reduction of aggregated alpha synuclein in ISF and/or CSF of the subject.

In one embodiment, the dosage regimen achieves a GM37v2 concentration which is at above the estimated IC50 in ISF and/or CSF of the subject.

In one embodiment, the dosage regimen achieves an GM37v2 concentration which is above the estimated IC50 and below the estimated IC95 for oligomeric alpha synuclein in ISF and/or CSF of the subject.

In one embodiment, the dosage regimen achieves a GM37v2 concentration which is above the estimated IC85 for oligomeric alpha synuclein and below the estimated IC95 in ISF and/or CSF of the subject.

In one embodiment, the dosage regimen achieves a GM37v2 concentration which is above the estimated IC85 for oligomeric alpha synuclein in the ISF and/or CSF of the subject.

In one embodiment, the dosage regimen achieves a GM37v2 concentration which is above the estimated IC90 for oligomeric alpha synuclein in the ISF and/or CSF of the subject.

In one embodiment, the dosage regimen achieves a GM37v2 concentration which is above the estimated IC95 for oligomeric alpha synuclein in the ISF and/or CSF of the subject.

In another embodiment, the dosage regimen achieves a GM37v2 concentration that is able to provide and maintain (after 1 or more doses) greater than estimated 50% reduction of aggregated a-synuclein in the ISF and/or CSF of the subject.

In another embodiment, the dosage regimen achieves a GM37v2 concentration that is able to provide and maintain (after 1 or more doses) greater than estimated 80% reduction of aggregated a-synuclein in the ISF and/or CSF of the subject.

In another embodiment, the dosage regimen achieves a GM37v2 concentration that is able to provide and maintain (after 1 or more doses) greater than estimated 90% reduction of aggregated a-synuclein in the ISF and/or CSF of the subject.

In another embodiment, the dosage regimen achieves a GM37v2 concentration that is able to provide and maintain (after 1 or more doses) greater than estimated 95% reduction of aggregated a-synuclein in the ISF and/or CSF of the subject.

The dosage regimens are relevant and apply to all types of synucleinopathies and prodromal synucleinopathies. Specifically, the dosing regimens are relevant for treating MSA, such as MSA-C, MSA-P, early MSA-P and/or early MSA-C, MSA in patients who are less impaired by the disease, MSA patients with a low UMSARS TS score at first dose administration, such as

below 40 (e.g., below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15). The dosage regimen is ultimately decided on the basis of the required estimated CSF mean steady state concentration needed to obtain the desired target engagement of oligomeric alpha synuclein in CSF/brain. Although it is not known exactly how much aggregated alpha synuclein must be removed from CSF/ISF to modify and/or slow disease progression, the CSF alpha synuclein load have not been found to differ significantly among different types of synucleinopathies. Tateno et al has e.g. shown that the amount of alpha synuclein in CSF is comparable between patient suffering from dementia with Lewy bodies (DLB), Parkinson disease (PD), and multiple system atrophy (MSA) (Tateno et al, Alzheimer Dis Assoc Disord 2012;26:213–216) which indicate that the dosage regimens can be predicted to be suitable for synucleinopathies generally and is therefore not limited to a specific indication such as PD, DLB or MSA.

In addition, the dosage regimens are also relevant for patients with prodromal synucleinopathies as these patients have been shown to display signs of altered alpha synuclein processing; e.g. Mollenhauer et al. has demonstrated that among prodromal synucleinopathy groups, the hyposmic participants showed the lowest mean CSF alpha synuclein levels, whereas iRBD participants had intermediate levels between healthy controls and Parkinson's Patients (Mollenhauer et al. Mov Disord. 2019 September; 34(9): 1354–1364). These findings indicate that patients with clinical traits of prodromal synucleinopathies already have decreased CSF alpha synuclein levels and this is consistent with significant pathology being present already during these prodromal stages.

Antibodies for use according to the invention.

The antibodies for use according to the present invention bind to an epitope within the 112-117 epitope. In one embodiment, the invention relates to monoclonal antibody GM37, its variants (e.g., GM37 Variant 1, GM37 Variant 2 and GM37 Variant 3), or GM285 for use in the treatment of synucleinopathies or prodromal synucleinopathies.

The GM37, GM37 Variant 1, GM37 Variant 2, and GM37 Variant 3 antibodies bind an epitope within amino acids 112-117 (**SEQ ID NO:9** (ILEDMP)) of human alpha synuclein (**SEQ ID**

NO:10). Specifically, the GM37, GM37 Variant 1, GM37 Variant 2, and GM37 Variant 3 antibodies bind all 6 amino acids within this epitope.

The GM285 antibody binds the epitope of amino acid 112-115 (ILED; **SEQ ID NO:19**) of human alpha synuclein (**SEQ ID NO:10**).

An "anti-alpha synuclein antibody" or “alpha synuclein antibody” (used interchangeably) is an antibody which binds to alpha synuclein or an alpha synuclein fragment. The antibodies of the present invention specifically bind within the amino acids sequence of alpha synuclein corresponding to SEQ ID NOs 9 and/or 19.

The term antibody “GM37” is intended to include an antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:1, 2 and 3** and the Light Chain CDR1-3 as given in **SEQ ID Nos:4, 5 and 6**. In one embodiment, the antibody GM37 may comprise the heavy chain variable domain of **SEQ ID NO:7** and/or the light chain variable domain of **SEQ ID NO:8**. For example, the antibody GM37 may be an IgG antibody comprising a heavy chain consisting of a variable domain **of SEQ ID NO:7** and a constant domain of **SEQ ID NO:18** together with a light chain consisting of a variable domain of **SEQ ID NO:8** and a kappa constant domain of **SEQ ID NO:17**.

The term antibody “GM37 variant 1” is intended to include an antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:1, 33 and 3** and the Light Chain CDR1-3 as given in **SEQ ID Nos:4, 5 and 6**. In one embodiment, the antibody GM37 variant 1 may comprise the heavy chain variable domain of **SEQ ID NO:30** and/or the light chain variable domain of **SEQ ID NO:8**. For example, the antibody GM37 variant 1 may be an IgG1 antibody comprising a heavy chain consisting of a variable domain **of SEQ ID NO:30** and a constant domain of **SEQ ID NO:18** together with a light chain consisting of a variable domain of **SEQ ID NO:8** and a kappa constant domain of **SEQ ID NO:17**.

The term antibody “GM37 variant 2” or “GM37v2” or “GM37var2” (used interchangeably) is intended to include an antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:1, 34 and 3** and the Light Chain CDR1-3 as given in **SEQ ID Nos:4, 5 and 6**. In one embodiment, the antibody GM37 variant 2 comprise the heavy chain variable domain of **SEQ ID NO:31** and the light chain variable domain of **SEQ ID NO:8**.

For example, the antibody GM37 variant 2 may be an IgG1 antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:1, 34 and 3** and the Light Chain CDR1-3 as given in **SEQ ID Nos:4, 5 and 6**.

For example, the antibody GM37 variant 2 may be a human IgG1 antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:1, 34 and 3** and the Light Chain CDR1-3 as given in **SEQ ID Nos:4, 5 and 6**.

For example, the antibody GM37 variant 2 may be an IgG1 antibody comprising a variable heavy chain domain of **SEQ ID NO:31** and variable light chain domain of **SEQ ID NO:8**.

For example, the antibody GM37 variant 2 may be a human IgG1 antibody comprising a variable heavy chain domain of **SEQ ID NO:31** and variable light chain domain of **SEQ ID NO:8**.

For example, the antibody GM37 variant 2 may be an IgG1 antibody comprising a variable heavy chain domain of **SEQ ID NO:31** and a heavy chain constant domain of **SEQ ID NO:18** together with a variable light chain domain of **SEQ ID NO:8** and a kappa light chain constant domain of **SEQ ID NO:17**.

For example, the antibody GM37 variant 2 may be a human IgG1 antibody comprising a variable heavy chain domain of **SEQ ID NO:31** and a heavy chain constant domain of **SEQ ID NO:18** together with a variable light chain domain of **SEQ ID NO:8** and a kappa light chain constant domain of **SEQ ID NO:17**.

In a preferred embodiment, the antibody GM37 variant 2 is Amlenetug.

The term antibody "GM37 variant 3" is intended to include an antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:1, 35 and 3** and the Light Chain CDR1-3 as given in **SEQ ID Nos:4, 5 and 6**. In one embodiment, the antibody GM37 variant 3 may comprise the heavy chain variable domain of **SEQ ID NO:32** and/or the light chain variable domain of **SEQ ID NO:8**. For example, the antibody GM37 variant 3 may be an IgG1 antibody comprising a heavy chain consisting of a variable domain **of SEQ ID NO:32** and a constant domain of **SEQ ID NO:18** together with a light chain consisting of a variable domain of **SEQ ID NO:8** and a kappa constant domain of **SEQ ID NO:17**.

The term antibody "GM285" is intended to include an antibody comprising the Heavy Chain CDR1-3 **SEQ ID Nos:20, 21 and 22** and the Light Chain CDR1-3 as given in **SEQ ID Nos:23, 24 and 25**. In one embodiment, the antibody GM285 may comprise the heavy chain variable domain of **SEQ ID NO:26** and/or the light chain variable domain of **SEQ ID NO:27**. For example, the antibody GM285 may be an IgG1 antibody comprising a heavy chain consisting of a variable domain **of SEQ ID NO:26** and a constant domain of **SEQ ID NO:28** together with a light chain consisting of a variable domain of **SEQ ID NO:27** and a kappa constant domain of **SEQ ID NO:29**.

In preferred embodiments the full-length GM37, GM37 Variant 1, GM37 Variant 2, GM37 Variant 3, or GM285 antibody is an IgG isotype format, most preferred is the IgG1 format, even more preferred is a human or humanized IgG1 format. Most preferred is a human GM37v2 IgG1 format.

Table with specific amino acid sequences anti-alpha synuclein antibodies as used herein:

SEQ ID NO:1	GM37 CDR 1 Heavy Chain
SEQ ID NO:2	GM37 CDR 2 Heavy Chain
SEQ ID NO:3	GM37 CDR 3 Heavy Chain
SEQ ID NO:4	GM37 CDR 1 Light Chain
SEQ ID NO:5	GM37 CDR 2 Light Chain
SEQ ID NO:6	GM37 CDR 3 Light Chain
SEQ ID NO:7	GM37 Heavy Chain Variable Domain
SEQ ID NO:8	GM37 Light Chain Variable Domain
SEQ ID NO:9	Epitope 112-117 of Human Alpha synuclein
SEQ ID NO:10	Human Alpha synuclein
SEQ ID NO:11	A-Syn-AAKK-BAP
SEQ ID NO:12	A-Syn-BAAK-BAP
SEQ ID NO:13	A-Syn-BBAA-BAP
SEQ ID NO:14	A-Syn-BBKK-BAP
SEQ ID NO:15	A-Syn-120-140_Del-BAP
SEQ ID NO:16	Residues 1-119 of Human Alpha synuclein
SEQ ID NO:17	Kappa Light Chain Constant domain
SEQ ID NO:18	IgG1 Heavy Chain Constant domain
SEQ ID NO:19	GM285 Epitope 112-115
SEQ ID NO:20	GM285 CDR 1 Heavy Chain
SEQ ID NO:21	GM285 CDR 2 Heavy Chain
SEQ ID NO:22	GM285 CDR 3 Heavy Chain
SEQ ID NO:23	GM285 CDR 1 Light Chain
SEQ ID NO:24	GM285 CDR 2 Light Chain
SEQ ID NO:25	GM285 CDR 3 Light Chain
SEQ ID NO:26	GM285 Heavy Chain Variable Domain
SEQ ID NO:27	GM285 Light Chain Variable Domain
SEQ ID NO:28	GM285 IgG1 Heavy Chain Constant domain
SEQ ID NO:29	GM285 Kappa Light Chain Constant domain
SEQ ID NO:30	GM37 Variant 1 Heavy Chain Variable Domain
SEQ ID NO:31	GM37 Variant 2 Heavy Chain Variable Domain
SEQ ID NO:32	GM37 Variant 3 Heavy Chain Variable Domain
SEQ ID NO:33	GM37 Variant 1 Heavy Chain CDR 2
SEQ ID NO:34	GM37 Variant 2 Heavy Chain CDR 2
SEQ ID NO:35	GM37 Variant 3 Heavy Chain CDR 2
SEQ ID NO:36	9E4 Binding Epitope
SEQ ID NO:37	Human Beta-Synuclein
SEQ ID NO:38	Human Gamma-Synuclein
SEQ ID NO:39	Alpha synuclein Ortholog for Cynomolgus Monkey
SEQ ID NO:40	Alpha synuclein Ortholog for Rat
SEQ ID NO:41	Alpha synuclein Ortholog for Mouse
SEQ ID NO:42	9E4 HC
SEQ ID NO:43	9E4 LC

Specific amino acid sequences used herein:

GFTFSSYAMT (**SEQ ID NO:1**)
AIRSN GDRTD YADSVKG (**SEQ ID NO:2**)
AIRSS GDRTD YADSVKG (**SEQ ID NO:33**)
AIRSQ GDRTD YADSVKG (**SEQ ID NO:34**)
AIRSH GDRTD YADSVKG (**SEQ ID NO:35**)
AKNWAPFDS (**SEQ ID NO:3**)
ASQSVSSSYLA (**SEQ ID NO:4**)

GASSRAT (**SEQ ID NO:5**)

QQYGSSPWT (**SEQ ID NO:6**)

EVQLLESGGG LVQTGGSLRL SCAASGFTFS SYAMTWVRQA PGKGLEWVSA IRSNGDRTDY ADSVKGRFTI SRDNSQNTLY LQMNSLRAED TAVYYCAKNW APFDSWGQGT LVTVSS (**SEQ ID NO:7**)

EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIK (**SEQ ID NO:8**)

EVQLLESGGG LVQPGGSLRL SCAASGFTFS RFTMTWVRQA PGKGLEWVSA ISGSGGGTSY ADSVKGRLTV SRDNSKNTLY LQMNSLRAED TAVYYCAKNW APFDYWGQGT LVTVSS (**SEQ ID NO 26**).

EIVLTQSPGT LSLSPGERAT LSCRASQSVS RSYLAWYQQK PGQAPRLLIY GASSRATGIP DRFSGSGSGT DFTLTVSRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIK (**SEQ ID NO:27**).

EVQLLESGGG LVQTGGSLRL SCAASGFTFS SYAMTWVRQA PGKGLEWVSA IRSSGDRTDY ADSVKGRFTI SRDNSQNTLY LQMNSLRAED TAVYYCAKNW APFDSWGQGT LVTVSS (**SEQ ID NO:30**)

EVQLLESGGG LVQTGGSLRL SCAASGFTFS SYAMTWVRQA PGKGLEWVSA IRSQGDRTDY ADSVKGRFTI SRDNSQNTLY LQMNSLRAED TAVYYCAKNW APFDSWGQGT LVTVSS (**SEQ ID NO:31**)

EVQLLESGGG LVQTGGSLRL SCAASGFTFS SYAMTWVRQA PGKGLEWVSA IRSHGDRTDY ADSVKGRFTI SRDNSQNTLY LQMNSLRAED TAVYYCAKNW APFDSWGQGT LVTVSS (**SEQ ID NO:32**)

RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD
SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC **(SEQ ID NO:17)**

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPG **(SEQ ID NO:18)**

AASGFTFSRFTMT (**SEQ ID NO:20**)

AISGSGGGTS YADSVKG (**SEQ ID NO:21**)

AKNWAPFDY (**SEQ ID NO:22**)

RASQSVSRSYLA (**SEQ ID NO:23**)

GASSRAT (**SEQ ID NO:24**)

QQYGSSPWT (**SEQ ID NO:25**)

Full sequence list is given below:

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Sequence Listing Information:
       DTD Version: V1_3
       File Name: 1294-WO-PCT Seq list ST26.xml
       Software Name: WIPO Sequence
       Software Version: 2.3.0
       Production Date: 2025-02-21
General Information:
       Current application / IP Office: WO
       Current application / Applicant file reference: 1294-WO-PCT
       Applicant name: H. Lundbeck A/S
       Applicant name / Language: en
       Applicant name / Name Latin: H. Lundbeck A/S
       Invention title: COMPOSITIONS AND METHODS FOR TREATING MULTIPLE SYSTEM
ATROPHY (MSA) ( en )
       Sequence Total Quantity: 43

Sequences:
       Sequence Number (ID): 1
       Length: 10
       Molecule Type: AA
       Features Location/Qualifiers:
              - REGION, 1..10
                     > note, GM37 CDR 1 Heavy Chain
              - source, 1..10
                     > mol_type, protein
                     > organism, synthetic construct
       Residues:
       GFTFSSYAMT                                                        10

       Sequence Number (ID): 2
       Length: 17
       Molecule Type: AA
       Features Location/Qualifiers:
              - REGION, 1..17
                     > note, GM37 CDR2 Heavy Chain
              - source, 1..17
                     > mol_type, protein
                     > organism, synthetic construct
       Residues:
       AIRSNGDRTD  YADSVKG                                               17

       Sequence Number (ID): 3
       Length: 9
       Molecule Type: AA
       Features Location/Qualifiers:
              - REGION, 1..9
                     > note, GM37 CDR3 Heavy Chain
              - source, 1..9
                     > mol_type, protein
                     > organism, synthetic construct
       Residues:
       AKNWAPFDS                                                         9

       Sequence Number (ID): 4
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Length: 11
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..11
> note, GM37 CDR1 Light Chain
- source, 1..11
> mol_type, protein
> organism, synthetic construct
Residues:
ASQSVSSSYL A 11

Sequence Number (ID): 5
Length: 7
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..7
> note, GM37 CDR 2 Light Chain
- source, 1..7
> mol_type, protein
> organism, synthetic construct
Residues:
GASSRAT 7

Sequence Number (ID): 6
Length: 9
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..9
> note, GM37 CDR 3 Light Chain
- source, 1..9
> mol_type, protein
> organism, synthetic construct
Residues:
QQYGSSPWT 9

Sequence Number (ID): 7
Length: 116
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..116
> note, GM37 CDR Heavy Chain
- source, 1..116
> mol_type, protein
> organism, synthetic construct
Residues:
EVQLLESGGG LVQTGGSLRL SCAASGFTFS SYAMTWVRQA PGKGLEWVSA IRSNGDRTDY 60
ADSVKGRFTI SRDNSQNTLY LQMNSLRAED TAVYYCAKNW APFDSWGQGT LVTVSS 116

Sequence Number (ID): 8
Length: 108
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..108
> note, GM 37 Light Chain
- source, 1..108
> mol_type, protein
> organism, synthetic construct
Residues:
EIVLTQSPGT LSLSPGERAT LSCRASQSVS SSYLAWYQQK PGQAPRLLIY GASSRATGIP 60
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIK 108

Sequence Number (ID): 9
Length: 6
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..6
> note, Epitope 112-117
- source, 1..6
> mol_type, protein
> organism, synthetic construct
Residues:
ILEDMP 6

Sequence Number (ID): 10
Length: 140
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..140
> note, Alpha synuclein

- source, 1..140
  > mol_type, protein
  > organism, synthetic construct

Residues:
MDVFMKGLSK AKEGVVAAAE KTKQGVAEAA GKTKEGVLYV GSKTKEGVVH GVATVAEKTK 60
EQVTNVGGAV VTGVTAVAQK TVEGAGSIAA ATGFVKKDQL GKNEEGAPQE GILEDMPVDP 120
DNEAYEMPSE EGYQDYEPEA 140

Sequence Number (ID): 11
Length: 165
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..165
  > note, A-Syn-AAKK-BAP
- source, 1..165
  > mol_type, protein
  > organism, synthetic construct

Residues:
MDVFMKGLSK AKEGVVAAAE KTKQGVAEAA GKTKEGVLYV GSKTKEGVVH GVATVAEKTK 60
EQVTNVGGAV VTGVTAVAQK TVEGAGNIAA ATGLVKKDQL AKQNEEGFLQ EGMVNNTDIP 120
VDPENEAYEM PPEEEYQDYE PEAGSAGGSG GLNDIFEAQK IEWHE 165

Sequence Number (ID): 12
Length: 165
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..165
  > note, A-Syn-BAAK-BAP
- source, 1..165
  > mol_type, protein
  > organism, synthetic construct

Residues:
MDVFMKGLSM AKEGVVAAAE KTKQGVTEAA EKTKEGVLYV GSKTKEGVVH GVATVAEKTK 60
EQVTNVGGAV VTGVTAVAQK TVEGAGSIAA ATGFVKKDQL AKQNEEGFLQ EGMVNNTDIP 120
VDPENEAYEM PPEEEYQDYE PEAGSAGGSG GLNDIFEAQK IEWHE 165

Sequence Number (ID): 13
Length: 162
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..162
  > note, A-Syn-BBAA-BAP
- source, 1..162
  > mol_type, protein
  > organism, synthetic construct

Residues:
MDVFMKGLSM AKEGVVAAAE KTKQGVTEAA EKTKEGVLYV GSKTREGVVQ GVASVAEKTK 60
EQASHLGGAV VTGVTAVAQK TVEGAGSIAA ATGFVKKDQL GKNEEGAPQE GILEDMPVDP 120
DNEAYEMPSE EGYQDYEPEA GSAGGSGGLN DIFEAQKIEW HE 162

Sequence Number (ID): 14
Length: 165
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..165
  > note, A-Syn-BBKK-BAP
- source, 1..165
  > mol_type, protein
  > organism, synthetic construct

Residues:
MDVFMKGLSM AKEGVVAAAE KTKQGVTEAA EKTKEGVLYV GSKTREGVVQ GVASVAEKTK 60
EQASHLGGAV VTGVTAVAQK TVEGAGNIAA ATGLVKKDQL AKQNEEGFLQ EGMVNNTDIP 120
VDPENEAYEM PPEEEYQDYE PEAGSAGGSG GLNDIFEAQK IEWHE 165

Sequence Number (ID): 15
Length: 141
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..141
  > note, A-Syn-120-140_Del-BAP
- source, 1..141
  > mol_type, protein
  > organism, synthetic construct

Residues:
MDVFMKGLSK AKEGVVAAAE KTKQGVAEAA GKTKEGVLYV GSKTKEGVVH GVATVAEKTK 60
EQVTNVGGAV VTGVTAVAQK TVEGAGSIAA ATGFVKKDQL GKNEEGAPQE GILEDMPVDG 120
SAGGSGGLND IFEAQKIEWH E 141

Sequence Number (ID): 16

Length: 131
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..131
> note, alpha synuclein amino acids 1-119
- source, 1..131
> mol_type, protein
> organism, synthetic construct
Residues:
MAHHHHHHIE GRMDVFMKGL SKAKEGVVAA AEKTKQGVAE AAGKTKEGVL YVGSKTKEGV 60
VHGVATVAEK TKEQVTNVGG AVVTGVTAVA QKTVEGAGSI AAATGFVKKD QLGKNEEGAP 120
QEGILEDMPV D 131

Sequence Number (ID): 17
Length: 107
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..107
> note, kappa (LC constant region)
- source, 1..107
> mol_type, protein
> organism, synthetic construct
Residues:
RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD 60
SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC 107

Sequence Number (ID): 18
Length: 329
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..329
> note, IgG1 (HC Constant region)
- source, 1..329
> mol_type, protein
> organism, synthetic construct
Residues:
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPG 329

Sequence Number (ID): 19
Length: 4
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..4
> note, GM285 epitope 112-115
- source, 1..4
> mol_type, protein
> organism, synthetic construct
Residues:
ILED 4

Sequence Number (ID): 20
Length: 13
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..13
> note, GM285 CDR1 Heavy Chain
- source, 1..13
> mol_type, protein
> organism, synthetic construct
Residues:
AASGFTFSRF TMT 13

Sequence Number (ID): 21
Length: 17
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..17
> note, GM285 CDR2 Heavy Chain
- source, 1..17
> mol_type, protein
> organism, synthetic construct
Residues:
AISGSGGGTS YADSVKG 17

Sequence Number (ID): 22
Length: 9
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..9
> note, GM285 CDR3 Heavy Chain
- source, 1..9
> mol_type, protein
> organism, synthetic construct
Residues:
AKNWAPFDY 9

Sequence Number (ID): 23
Length: 12
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..12
> note, GM285 CDR1 Light Chain
- source, 1..12
> mol_type, protein
> organism, synthetic construct
Residues:
RASQSVSRSY LA 12

Sequence Number (ID): 24
Length: 7
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..7
> note, GM285 CDR2 Light Chain
- source, 1..7
> mol_type, protein
> organism, synthetic construct
Residues:
GASSRAT 7

Sequence Number (ID): 25
Length: 9
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..9
> note, GM285 CDR3 Light Chain
- source, 1..9
> mol_type, protein
> organism, synthetic construct
Residues:
QQYGSSPWT 9

Sequence Number (ID): 26
Length: 116
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..116
> note, GM285 VH
- source, 1..116
> mol_type, protein
> organism, synthetic construct
Residues:
EVQLLESGGG LVQPGGSLRL SCAASGFTFS RFTMTWVRQA PGKGLEWVSA ISGSGGGTSY 60
ADSVKGRLTV SRDNSKNTLY LQMNSLRAED TAVYYCAKNW APFDYWGQGT LVTVSS 116

Sequence Number (ID): 27
Length: 108
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..108
> note, GM285 VL
- source, 1..108
> mol_type, protein
> organism, synthetic construct
Residues:
EIVLTQSPGT LSLSPGERAT LSCRASQSVS RSYLAWYQQK PGQAPRLLIY GASSRATGIP 60
DRFSGSGSGT DFTLTVSRLE PEDFAVYYCQ QYGSSPWTFG QGTKVEIK 108

Sequence Number (ID): 28
Length: 329
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..329

> note, GM285 IgG1 constant region
- source, 1..329
> mol_type, protein
> organism, synthetic construct

Residues:

ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK	DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	60
GLYSLSSVVT	VPSSSLGTQT	YICNVNHKPS	NTKVDKRVEP	KSCDKTHTCP	PCPAPELLGG	120
PSVFLFPPKP	KDTLMISRTP	EVTCVVVDVS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN	180
STYRVVSVLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ	VYTLPPSREE	240
MTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV	LDSDGSFFLY	SKLTVDKSRW	300
QQGNVFSCSV	MHEALHNHYT	QKSLSLSPG				329

Sequence Number (ID): 29
Length: 106
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..106
> note, GM285 Kappa chain
- source, 1..106
> mol_type, protein
> organism, synthetic construct

Residues:

TVAAPSVFIF	PPSDEQLKSG	TASVVCLLNN	FYPREAKVQW	KVDNALQSGN	SQESVTEQDS	60
KDSTYSLSST	LTLSKADYEK	HKVYACEVTH	QGLSSPVTKS	FNRGEC		106

Sequence Number (ID): 30
Length: 116
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..116
> note, GM37 Variant 1 heavy chain
- source, 1..116
> mol_type, protein
> organism, synthetic construct

Residues:

EVQLLESGGG	LVQTGGSLRL	SCAASGFTFS	SYAMTWVRQA	PGKGLEWVSA	IRSSGDRTDY	60
ADSVKGRFTI	SRDNSQNTLY	LQMNSLRAED	TAVYYCAKNW	APFDSWGQGT	LVTVSS	116

Sequence Number (ID): 31
Length: 116
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..116
> note, GM 37 variant 2 heavy chain
- source, 1..116
> mol_type, protein
> organism, synthetic construct

Residues:

EVQLLESGGG	LVQTGGSLRL	SCAASGFTFS	SYAMTWVRQA	PGKGLEWVSA	IRSQGDRTDY	60
ADSVKGRFTI	SRDNSQNTLY	LQMNSLRAED	TAVYYCAKNW	APFDSWGQGT	LVTVSS	116

Sequence Number (ID): 32
Length: 116
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..116
> note, GM 37 variant 3 heavy chain
- source, 1..116
> mol_type, protein
> organism, synthetic construct

Residues:

EVQLLESGGG	LVQTGGSLRL	SCAASGFTFS	SYAMTWVRQA	PGKGLEWVSA	IRSHGDRTDY	60
ADSVKGRFTI	SRDNSQNTLY	LQMNSLRAED	TAVYYCAKNW	APFDSWGQGT	LVTVSS	116

Sequence Number (ID): 33
Length: 17
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..17
> note, GM37 variant 1 heavy chain CDR 2
- source, 1..17
> mol_type, protein
> organism, synthetic construct

Residues:

AIRSSGDRTD	YADSVKG					17

Sequence Number (ID): 34
Length: 17
Molecule Type: AA

Features Location/Qualifiers:
- REGION, 1..17
> note, GM37 variant 2 CDR 2 heavy chain
- source, 1..17
> mol_type, protein
> organism, synthetic construct
Residues:
AIRSQGDRTD YADSVKG 17

Sequence Number (ID): 35
Length: 17
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..17
> note, GM37 variant 3 CDR 2 heavy chain
- source, 1..17
> mol_type, protein
> organism, synthetic construct
Residues:
AIRSHGDRTD YADSVKG 17

Sequence Number (ID): 36
Length: 5
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..5
> note, 9E4 binding epitope
- source, 1..5
> mol_type, protein
> organism, synthetic construct
Residues:
NEAYE 5

Sequence Number (ID): 37
Length: 134
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..134
> note, HUMAN Beta-synuclein
- source, 1..134
> mol_type, protein
> organism, synthetic construct
Residues:
MDVFMKGLSM AKEGVVAAAE KTKQGVTEAA EKTKEGVLYV GSKTREGVVQ GVASVAEKTK 60
EQASHLGGAV FSGAGNIAAA TGLVKREEFP TDLKPEEVAQ EAAEEPLIEP LMEPEGESYE 120
DPPQEEYQEY EPEA 134

Sequence Number (ID): 38
Length: 127
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..127
> note, HUMAN Gamma-synuclein
- source, 1..127
> mol_type, protein
> organism, synthetic construct
Residues:
MDVFKKGFSI AKEGVVGAVE KTKQGVTEAA EKTKEGVMYV GAKTKENVVQ SVTSVAEKTK 60
EQANAVSEAV VSSVNTVATK TVEEAENIAV TSGVVRKEDL RPSAPQQEGE ASKEKEEVAE 120
EAQSGGD 127

Sequence Number (ID): 39
Length: 140
Molecule Type: AA
Features Location/Qualifiers:
- REGION, 1..140
> note, alpha synuclein ortholog for Cynomolgus monkey
- source, 1..140
> mol_type, protein
> organism, synthetic construct
Residues:
MDVFMKGLSK AKEGVVAAAE KTKQGVAEAA GKTKEGVLYV GSKTKEGVVH GVATVAEKTK 60
EQVTNVGGAV VTGVTAVAQK TVEGAGSIAA ATGFIKKDQL GKNEEGAPQE GILQDMPVDP 120
DNEAYEMPSE EGYQDYEPEA 140

Sequence Number (ID): 40
Length: 140
Molecule Type: AA
Features Location/Qualifiers:

```
            - REGION, 1..140
                  > note, alpha synuclein ortholog for Rat
            - source, 1..140
                  > mol_type, protein
                  > organism, synthetic construct
      Residues:
      MDVFMKGLSK  AKEGVVAAAE  KTKQGVAEAA  GKTKEGVLYV  GSKTKEGVVH  GVTTVAEKTK  60
      EQVTNVGGAV  VTGVTAVAQK  TVEGAGNIAA  ATGFVKKDQM  GKGEEGYPQE  GILEDMPVDP  120
      SSEAYEMPSE  EGYQDYEPEA                                                 140

      Sequence Number (ID): 41
      Length: 140
      Molecule Type: AA
      Features Location/Qualifiers:
            - REGION, 1..140
                  > note, alpha synuclein ortholog for Mouse
            - source, 1..140
                  > mol_type, protein
                  > organism, synthetic construct
      Residues:
      MDVFMKGLSK  AKEGVVAAAE  KTKQGVAEAA  GKTKEGVLYV  GSKTKEGVVH  GVTTVAEKTK  60
      EQVTNVGGAV  VTGVTAVAQK  TVEGAGNIAA  ATGFVKKDQM  GKGEEGYPQE  GILEDMPVDP  120
      GSEAYEMPSE  EGYQDYEPEA                                                 140

      Sequence Number (ID): 42
      Length: 446
      Molecule Type: AA
      Features Location/Qualifiers:
            - REGION, 1..446
                  > note, 9E4 HC
            - source, 1..446
                  > mol_type, protein
                  > organism, synthetic construct
      Residues:
      EVQLVESGGG  LVQPGGSLRL  SCAASGFTFS  NYGMSWVRQA  PGKGLEWVAS  ISSGGGSTYY  60
      PDNVKGRFTI  SRDNAKNSLY  LQMNSLRAED  TAVYYCARGG  AGIDYWGQGT  LVTVSSASTK  120
      GPSVFPLAPS  SKSTSGGTAA  LGCLVKDYFP  EPVTVSWNSG  ALTSGVHTFP  AVLQSSGLYS  180
      LSSVVTVPSS  SLGTQTYICN  VNHKPSNTKV  DKRVEPKSCD  KTHTCPPCPA  PELLGGPSVF  240
      LFPPKPKDTL  MISRTPEVTC  VVVDVSHEDP  EVKFNWYVDG  VEVHNAKTKP  REEQYNSTYR  300
      VVSVLTVLHQ  DWLNGKEYKC  KVSNKALPAP  IEKTISKAKG  QPREPQVYTL  PPSREEMTKN  360
      QVSLTCLVKG  FYPSDIAVEW  ESNGQPENNY  KTTPPVLDSD  GSFFLYSKLT  VDKSRWQQGN  420
      VFSCSVMHEA  LHNHYTQKSL  SLSPGK                                         446

      Sequence Number (ID): 43
      Length: 220
      Molecule Type: AA
      Features Location/Qualifiers:
            - REGION, 1..220
                  > note, 9E4 LC
            - source, 1..220
                  > mol_type, protein
                  > organism, synthetic construct
      Residues:
      DIQMTQSPSS  LSASVGDRVT  ITCKSIQTLL  YSSNQKNYLA  WFQQKPGKAP  KLLIYWASIR  60
      KSGVPSRFSG  SGSGTDFTLT  ISSLQPEDLA  TYYCQQYYSY  PLTFGGGTKL  EIKRTVAAPS  120
      VFIFPPSDEQ  LKSGTASVVC  LLNNFYPREA  KVQWKVDNAL  QSGNSQESVT  EQDSKDSTYS  180
      LSSTLTLSKA  DYEKHKVYAC  EVTHQGLSSP  VTKSFNRGEC                          220
END
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The antibodies for use according to the present invention may be obtained from any suitable source and may in some embodiments be produced in different cell lines, such as be produced in a human cell line, a mammal non-human cell line, or insect cell line, for example be produced in a CHO cell line, a HEK cell line, a BHK-21 cell line, a murine cell line (such as a myeloma cell line), a fibrosarcoma cell line, a PER.C6 cell line, a HKB-11 cell line, a CAP cell line or a HuH-7 human cell line.

In one embodiment, the antibody for use according to the invention is a human antibody. Human monoclonal antibodies directed against alpha synuclein may be generated using

transgenic or transchromosomal mice carrying parts of the human immune system rather than the mouse system. Such transgenic and transchromosomic mice include mice may be referred to as HuMAb mice and KM mice, respectively.

In one embodiment the antibodies for use according to the present invention, exemplified by GM37 its variants GM37 var 1-3 and GM285 are capable of binding the toxic alpha synuclein fragments consisting of residues 1-119/122 of alpha synuclein and neutralizing its toxicity (for example, by extracellular binding to the alpha synuclein fragment and thereby preventing it from being taken up by cells). In a further embodiment the antibodies for use according to the present invention, are capable of binding to an epitope within amino acids 112-117 of alpha synuclein and binds toxic alpha synuclein species in human brain. In a further embodiment the antibodies for use according to the present invention have effects on clearing extracellular alpha synuclein and normalizing an impaired synaptic transmission induced by alpha synuclein in vivo. In yet another embodiment the antibodies for use according to the invention are also able to ameliorate the appearance of a relevant motor phenotype in a rat model for Parkinson's disease. All these properties are described in detail in WO2017/009312.

Pharmaceutical formulations and administration routes

A pharmaceutical composition for use according to the present invention may include diluents, fillers, salts, buffers, detergents (e.g., a non-ionic detergent, such as Tween-20 or Tween- 80), stabilizers (e.g., sugars or protein-free amino acids), preservatives, tissue fixatives, solubilizers, and/or other materials suitable for inclusion in a pharmaceutical composition.

In addition, the pharmaceutical composition or formulation may also include other carriers, or non-toxic, nontherapeutic, non-immunogenic stabilizers and the like. The compositions may also include large, slowly metabolized macromolecules, such as proteins, polysaccharides like chitosan, polylactic acids, polyglycolic acids and copolymers (e.g., latex functionalized sepharose, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (e.g., oil droplets or liposomes).

Pharmaceutically acceptable carriers include any and all suitable solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonicity agents, antioxidants and absorption delaying agents, and the like that are physiologically compatible with an antibody for use

according to the invention. Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the present invention include water, saline, phosphate buffered saline, ethanol, dextrose, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, corn oil, peanut oil, cottonseed oil, and sesame oil, carboxymethyl cellulose colloidal solutions, tragacanth gum and organic esters, such as ethyl oleate, and/or various buffers. Other carriers are well known in the pharmaceutical arts and may also be employed in the present invention.

Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile solutions.

Pharmaceutical compositions of the present invention may also comprise pharmaceutically acceptable antioxidants for instance (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha- tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Pharmaceutical compositions of the present invention may also comprise isotonicity agents, such as sugars, polyalcohols, such as mannitol, sorbitol, glycerol or sodium chloride in the compositions.

The pharmaceutical compositions of the present invention may also contain one or more adjuvants appropriate for the chosen route of administration such as preservatives, wetting agents, emulsifying agents, dispersing agents, preservatives or buffers, which may enhance the shelf life or effectiveness of the pharmaceutical composition.

The antibodies of the present invention may be prepared with carriers that will protect the antibody against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Such carriers may include gelatin, glyceryl monostearate, glyceryl distearate, biodegradable, biocompatible polymers such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid alone or with a wax, or other materials well known in the art. Methods for the preparation of such formulations are generally known to those skilled in the art.

Pharmaceutical compositions for infusion must typically be sterile and stable under the conditions of manufacture and storage. The composition may be formulated as a solution, micro-emulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier may be an aqueous or non-aqueous solvent or dispersion medium containing for instance water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and organic esters, such as ethyl oleate.

Sterile solutions for infusion may be prepared by incorporating the active antibody in the required amount in an appropriate solvent with one or a combination of ingredients e.g. as enumerated above, as required, followed by sterilization microfiltration. Generally, dispersions are prepared by incorporating the active antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients e.g. from those enumerated above. In the case of sterile powders for the preparation of sterile solutions, examples of methods of preparation are vacuum drying and freeze-drying (lyophilization) that yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Compositions may be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active antibody which produce the desired therapeutic effect in association with the required pharmaceutical excipients.

In a particular embodiment the pharmaceutical composition is administered by intravenous infusion.

Specific liquid pharmaceutical compositions

In an aspect the antibody for use according to the invention is formulated as a liquid pharmaceutical composition and administered by intravenous infusion.

In one aspect the present invention provides use of a liquid pharmaceutical composition comprising a full length IgG1 monoclonal anti-alpha synuclein antibody in a concentration of about 20-230 mg/mL, such as 25-225 mg/mL, wherein said antibody 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**;

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**;

and wherein the composition further comprises a buffering agent, a pharmaceutically acceptable tonicity agent, a pharmaceutically acceptable surfactant and wherein the pH of the composition is between 4.5 to 7.5, such as 5.0 to 7.0, such as 5.5. to 6.5, such as 6.0.

In a preferred embodiment the liquid pharmaceutical composition for use according to the invention is a stable liquid pharmaceutical composition. In a preferred embodiment the liquid pharmaceutical composition is a low viscosity liquid pharmaceutical composition. In a preferred embodiment the liquid pharmaceutical composition is a stable and low viscosity liquid pharmaceutical composition. In a preferred embodiment the liquid pharmaceutical composition is suitable for clinical use and safe for patients in need of administration/dosing of the liquid pharmaceutical composition.

In certain embodiments the monoclonal anti-alpha synuclein antibody of the liquid pharmaceutical composition further comprises a heavy chain variable domain consisting of **SEQ ID NO:31** and a light chain variable domain consisting of **SEQ ID NO:8**. In a more specific embodiment the monoclonal anti-alpha synuclein antibody further comprises a constant heavy chain domain as defined in **SEQ ID NO:18** and a kappa light chain constant domain as defined in **SEQ ID NO:17**.

In some embodiment the liquid pharmaceutical composition comprises the monoclonal anti-alpha synuclein antibody at a concentration of more than 20 mg/mL, and in some embodiment, at a concentration of less than 230 mg/mL. In further embodiments the concentration of the monoclonal anti-alpha synuclein antibody in the pharmaceutical composition is between 20-225 mg/mL 20-220 mg/mL, 20-215 mg/mL, 20-210 mg/mL, 20-

205 mg/mL, 20-200 mg/mL, 20-195 mg/mL, 20-190 mg/mL, 20-185 mg/mL, 20-180 mg/mL, 20-175 mg/mL, 20-170 mg/mL, 20-165 mg/mL, 20-160 mg/mL, 20-155 mg/mL, 20-150 mg/mL, 20-145 mg/mL, 20-140 mg/mL, 20-135 mg/mL, 20-130 mg/mL, 20-125 mg/mL, 20-120 mg/mL, 20-115 mg/mL, 20-110 mg/mL, 20-105 mg/mL, 20-100 mg/mL, 20-95 mg/mL, 20-90 mg/mL, 20-85 mg/mL, 20-80 mg/mL, 20-75 mg/mL, 20-70 mg/mL, 20-65 mg/mL, 20-60 mg/mL, 20-55 mg/mL, 20-50 mg/mL, 20-45 mg/mL, 20-40 mg/mL, 20-35 mg/mL, 20-30 mg/mL, 20-25 mg/mL, 25-230 mg/mL, 30-230 mg/mL, 35-230 mg/mL, 40-230 mg/mL, 45-230 mg/mL, 50-230 mg/mL, 55-230 mg/mL, 60-230 mg/mL, 65-230 mg/mL, 70-230 mg/mL, 75-230 mg/mL, 80-230 mg/mL, 85-230 mg/mL, 90-230 mg/mL, 95-230 mg/mL, 100-230 mg/mL, 105-230 mg/mL, 110-230 mg/mL, 115-230 mg/mL, 120-230 mg/mL, 125-230 mg/mL, 130-230 mg/mL, 135-230 mg/mL, 140-230 mg/mL, 145-230 mg/mL, 150-230 mg/mL, 155-230 mg/mL, 160-230 mg/mL, 165-230 mg/mL, 170-230 mg/mL, 175-230 mg/mL, 180-230 mg/mL, 185-230 mg/mL, 190-230 mg/mL, 195-230 mg/mL, 200-230 mg/mL, 205-230 mg/mL, 210-230 mg/mL, 215-230 mg/mL, 220-230 mg/mL, 225-230 mg/mL, 25-225 mg/mL, 30-220 mg/mL, 35-215 mg/mL, 40-210 mg/mL, 45-205 mg/mL, 50-200 mg/mL, 55-195 mg/mL, 60-190 mg/mL, 65-185 mg/mL, 70-180 mg/mL, 75-175 mg/mL, 80-170 mg/mL, 85-165 mg/mL, 90-160 mg/mL, 95-155 mg/mL, 100-150 mg/mL, 105-145 mg/mL, 110-140 mg/mL, 115-135 mg/mL or 120-130 mg/mL; including every value in between these numbers. In specific embodiments the liquid pharmaceutical composition comprises the monoclonal anti-alpha synuclein antibody at a concentration of about 50 mg/mL. In another specific embodiments the monoclonal anti-alpha synuclein antibody of the liquid pharmaceutical composition has a concentration of about 53 mg/mL. In some embodiment the monoclonal anti-alpha synuclein antibody of the liquid pharmaceutical composition has a concentration of within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10% of said values, such as +/- 8%, such as +/- 6%, such as +/- 5%, such as +/- 4%, such as +/- 3%, such as +/- 2.5%, such as +/- 2%, such as +/- 1.5%, such as +/- 1%, such as +/- 0.75%, such as +/- 0.5%, such as +/- 0.25%, such as +/- 0.1%, such as +/- 0.05%, such as +/- 0.025%, such as +/- 0.01%, such as +/- 0.0075%, such as +/- 0.005%, such as +/- 0.0025%, such as +/- 0.001% or such as +/- 0.0005%. In some embodiments of the present invention the buffering agent is a single buffering agent or a mixture of buffering agents. In a further embodiment the buffering agent is selected from Acetate, Citrate, Tartrate, Histidine, Glutamate, Phosphate, Tris, Glycine, Bicarbonate, Succinate, Sulfate or Nitrate buffers or a mixture thereof. In further embodiments the buffering agents are selected from sodium phosphate, histidine (such as L-Histidine), citric

acid, sodium citrate, sodium acetate or a mixture thereof. In a specific embodiment, the buffering agent is a Histidine buffer (such as L-Histidine) or a mixture of Histidine buffers. The Histidine buffer can be selected from Histidine buffers and mixtures thereof such as Histidine, L-Histidine, L-Histidine hydrochloride, L-Histidine monohydrochloride, L-Histidine monohydrate and L-Histidine hydrochloride monohydrate or mixtures thereof. In one preferred embodiment, the histidine buffer is a mixture of L-Histidine and L-Histidine monohydrochloride. In some preferred embodiments of the liquid pharmaceutical composition the buffering agent is present in a concentration between 10-60 mM, such as 15-55 mM, such as 20-50 mM, such as 20-45 mM, such as 20-40 mM, such as 25-40 mM, such as 10-40 mM, such as 15-35 mM, such as 20-30 mM or such as 25 mM. In some embodiment the buffering agent of the liquid pharmaceutical composition has a concentration of within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10% of said values, such as +/- 8%, such as +/- 6%, such as +/- 5%, such as +/- 4%, such as +/- 3%, such as +/- 2.5%, such as +/- 2%, such as +/- 1.5%, such as +/- 1%, such as +/- 0.75%, such as +/- 0.5%, such as +/- 0.25%, such as +/- 0.1%, such as +/- 0.05%, such as +/- 0.025%, such as +/- 0.01%, such as +/- 0.0075%, such as +/- 0.005%, such as +/- 0.0025%, such as +/- 0.001% or such as +/- 0.0005%.

In an embodiment the pH of the liquid pharmaceutical composition for use according to the invention is in the range from about 4.5 to about 7.5, such as 4.5 to about 6.5, such as 5.0 to 6.5, such as from about 5.5 to about 6.5, for example from 5.7 to 6.4, 5.8 to 6.3 or 5.9 to 6.2. In one embodiment the liquid pharmaceutical composition has a pH of 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5 or 7.0. Histidine buffers (such as L-histidine) are example of buffers that may be comprised in the liquid pharmaceutical composition that will control the pH in this range. In a preferred embodiment the pH of the liquid pharmaceutical composition is 6.0. In some embodiment the liquid pharmaceutical composition has a pH within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10% of said values, such as +/- 8%, such as +/- 6%, such as +/- 5%, such as +/- 4%, such as +/- 3%, such as +/- 2.5%, such as +/- 2%, such as +/- 1.5%, such as +/- 1%, such as +/- 0.75%, such as +/- 0.5%, such as +/- 0.25%, such as +/- 0.1%, such as +/- 0.05%, such as +/- 0.025%, such as +/- 0.01%, such as +/- 0.0075%, such as +/- 0.005%, such as +/- 0.0025%, such as +/- 0.001% or such as +/- 0.0005%.

In an embodiment the surfactant of the liquid pharmaceutical composition for use according to the invention is a non-ionic surfactant. In further embodiments, the surfactant is selected from the group consisting of polysorbate (for example, polysorbate 20 and polysorbate 80); poloxamer (e.g. poloxamer 188); Triton; Triton X-100; sodium dodecyl sulfate (SDS); sodium laurel sulfate; sodium octyl glycoside; lauryl-, myristyl-, linoleyl-, or stearyl-sulfobetaine; lauryl-, myristyl-, linoleyl- or stearyl-sarcosine; linoleyl-, myristyl-, or cetyl-betaine; lauroamidopropyl-, cocamidopropyl-, linoleamidopropyl-, myristamidopropyl-, palmidopropyl-, or isostearamidopropyl-betaine (e.g. lauroamidopropyl); myristamidopropyl-, palmidopropyl-, or isostearamidopropyldimethylamine; sodium methyl cocoyl-, or disodium methyl oleyl-taurate; polyethyl glycol, polypropyl glycol, and copolymers of ethylene and propylene glycol. In one specific embodiment, the pharmaceutically acceptable surfactant of the liquid pharmaceutical composition is polysorbate 80 also known as Tween 80. In some preferred embodiments of the liquid pharmaceutical composition the surfactant is present in an amount of between 0.001% to 0.10% (w/v), such as 0.005% to 0.08% (w/v), such as 0.008% to 0.06% (w/v), such as 0.01% to 0.05% (w/v), such as 0.015% to 0.05% (w/v), such as 0.01% to 0.05% (w/v), such as 0.01% to 0.03% (w/v) or such as 0.02% (w/v). In some embodiment the surfactant of the liquid pharmaceutical composition has a concentration of within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10% of said values, such as +/- 8%, such as +/- 6%, such as +/- 5%, such as +/- 4%, such as +/- 3%, such as +/- 2.5%, such as +/- 2%, such as +/- 1.5%, such as +/- 1%, such as +/- 0.75%, such as +/- 0.5%, such as +/- 0.25%, such as +/- 0.1%, such as +/- 0.05%, such as +/- 0.025%, such as +/- 0.01%, such as +/- 0.0075%, such as +/- 0.005%, such as +/- 0.0025%, such as +/- 0.001% or such as +/- 0.0005%.

In an embodiment the tonicity agent of the liquid pharmaceutical composition for use according to the invention is selected from Mannitol, Sorbitol, Lactose, Dextrose, Trehalose, Sodium Chloride, Potassium Chloride, Glycerol and Glycerine. In one specific embodiment, the tonicity agent is a suitable salt such as NaCl. In one specific embodiment, the tonicity agent of the liquid pharmaceutical composition is sodium chloride (NaCl). In some preferred embodiments of the liquid pharmaceutical composition the tonicity agent is present in a concentration of 10-150 mM, such as 20-140 mM, such as 30-130 mM, such as 40-120 mM, such as 50-110 mM, such as 60-110 mM, such as 70-110 mM, such as 80-110 mM, such as 90-110 mM or such as about 100 mM. In some embodiment the tonicity agent of the liquid

pharmaceutical composition has a concentration of within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10% of said values, such as +/- 8%, such as +/- 6%, such as +/- 5%, such as +/- 4%, such as +/- 3%, such as +/- 2.5%, such as +/- 2%, such as +/- 1.5%, such as +/- 1%, such as +/- 0.75%, such as +/- 0.5%, such as +/- 0.25%, such as +/- 0.1%, such as +/- 0.05%, such as +/- 0.025%, such as +/- 0.01%, such as +/- 0.0075%, such as +/- 0.005%, such as +/- 0.0025%, such as +/- 0.001% or such as +/- 0.0005%.

In an embodiment the liquid pharmaceutical composition for use according to the invention further comprises a bulking agent which is selected from Sugars and polyols (such as Sucrose, Trehalose, Glucose, Lactose, Sorbitol, Mannitol and Glycerol); Amino Acids (such as Arginine, Aspartic Acid, Glutamic acid, Lysine, Glycine, Glutamate, Histidine, Methionine or Alanine); or Polymers and proteins (such as Gelatin, PVP, PLGA, PEG, dextran, cyclodextrin and derivatives, starch derivatives, HSA or BSA). In one specific embodiment, the bulking agent is selected from Arginine, Glutamate, Sucrose, Glycine or Sorbitol. In one specific embodiment, the bulking agent is sucrose. In some preferred embodiments of the liquid pharmaceutical composition the bulking agent is present in a concentration of 20-200 mM, such as 25-180 mM, such as 30-170 mM, such as 35-160 mM, such as 40-150 mM, such as 45-140 mM, such as 50-130 mM, such as 60-130 mM, such as 65-120 mM, such as 70-120 mM, such as 75-120 mM, such as 80-110 mM, such as 85-110 mM, such as 90-110 mM, such as 95-110 mM, such as 95-105 mM or such as 100 mM. In some embodiment the bulking agent of the liquid pharmaceutical composition has a concentration of within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10% of said values, such as +/- 8%, such as +/- 6%, such as +/- 5%, such as +/- 4%, such as +/- 3%, such as +/- 2.5%, such as +/- 2%, such as +/- 1.5%, such as +/- 1%, such as +/- 0.75%, such as +/- 0.5%, such as +/- 0.25%, such as +/- 0.1%, such as +/- 0.05%, such as +/- 0.025%, such as +/- 0.01%, such as +/- 0.0075%, such as +/- 0.005%, such as +/- 0.0025%, such as +/- 0.001% or such as +/- 0.0005%.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises the monoclonal anti-alpha synuclein antibody, GM37v2, histidine buffer and sodium chloride (NaCl) at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 20-230 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 10-60 mM histidine buffer and 10-150 mM sodium chloride (NaCl) at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 40-60 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 20-30 mM histidine buffer and 90-110 mM sodium chloride (NaCl) at pH 5.5-6.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer and 100 mM sodium chloride (NaCl) at pH 6.0.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer and 100 mM sodium chloride (NaCl) at pH 6.0 or within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10%, such as +/- 5%, such as +/- 1%, such as +/- 0.5%, such as +/- 0.25% or such as +/- 0.1%.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises the monoclonal anti-alpha synuclein antibody, GM37v2, histidine buffer and polysorbate 80 (tween 80) at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 20-230 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 10-60 mM histidine buffer and polysorbate 80 (tween 80) in an amount of between 0.001% to 0.10% (w/v), at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 40-60 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 20-30 mM histidine buffer and polysorbate 80 (tween 80) in an amount of between 0.01% to 0.03% (w/v), at pH 5.5-6.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0 or within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10%, such as +/- 5%, such as +/- 1%, such as +/- 0.5%, such as +/- 0.25% or such as +/- 0.1%.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises the monoclonal anti-alpha synuclein antibody, GM37v2, histidine buffer, sodium chloride (NaCl) and polysorbate 80 (tween 80) at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 20-230 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 10-60 mM histidine buffer, 10-150 mM sodium chloride (NaCl) and polysorbate 80 (tween 80) in an amount of between 0.001% to 0.10% (w/v), at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 40-60 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 20-30 mM histidine buffer, 90-110 mM sodium chloride (NaCl) and polysorbate 80 (tween 80) in an amount of between 0.01% to 0.03% (w/v), at pH 5.5-6.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sodium chloride (NaCl) and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sodium chloride (NaCl) and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0 or within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10%, such as +/- 5%, such as +/- 1%, such as +/- 0.5%, such as +/- 0.25% or such as +/- 0.1%.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises the monoclonal anti-alpha synuclein antibody, GM37v2, histidine buffer, sodium chloride (NaCl) and sucrose at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 20-230 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 10-60 mM histidine buffer, 10-150 mM sodium chloride (NaCl) and 20-200 mM sucrose, at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 40-60 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 20-30 mM histidine buffer, 90-110 mM sodium chloride (NaCl) and 90-110 mM sucrose, at pH 5.5-6.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sodium chloride (NaCl) and 100 mM sucrose, at pH 6.0.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sodium chloride (NaCl) and 100 mM sucrose, at pH 6.0 or within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10%, such as +/- 5%, such as +/- 1%, such as +/- 0.5%, such as +/- 0.25% or such as +/- 0.1%.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises the monoclonal anti-alpha synuclein antibody, GM37v2, histidine buffer, sucrose and polysorbate 80 (tween 80) at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 20-230 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 10-60 mM histidine buffer, 20-200 mM sucrose and polysorbate 80 (tween 80) in an amount of between 0.001% to 0.10% (w/v), at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 40-60 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 20-30 mM histidine buffer, 90-110 mM sucrose and polysorbate 80 (tween 80) in an amount of between 0.01% to 0.03% (w/v), at pH 5.5-6.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sucrose and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sucrose and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0 or within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10%, such as +/- 5%, such as +/- 1%, such as +/- 0.5%, such as +/- 0.25% or such as +/- 0.1%.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises the monoclonal anti-alpha synuclein antibody, GM37v2, histidine buffer, sodium chloride (NaCl), sucrose and polysorbate 80 (tween 80) at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 20-230 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 10-60 mM histidine buffer, 10-150 mM sodium chloride (NaCl), 20-200 mM sucrose and polysorbate 80 (tween 80) in an amount of between 0.001% to 0.10% (w/v), at pH 4.5-7.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 40-60 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 20-30 mM histidine buffer, 90-110 mM sodium chloride (NaCl), 90-110 mM sucrose and polysorbate 80 (tween 80) in an amount of between 0.01% to 0.03% (w/v), at pH 5.5-6.5.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sodium chloride (NaCl), 100 mM sucrose and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0.

In an embodiment the liquid pharmaceutical composition for use according to the invention comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, GM37v2, 25 mM histidine buffer, 100 mM sodium chloride (NaCl), 100 mM sucrose and polysorbate 80 (tween 80) in an amount of 0.02% (w/v), at pH 6.0 or within +/- 30% of said values, such as +/- 25%, such as +/- 20%, such as +/- 15%, such as +/- 10%, such as +/- 5%, such as +/- 1%, such as +/- 0.5%, such as +/- 0.25% or such as +/- 0.1%.

In certain embodiments the liquid pharmaceutical composition for use according to the invention is presented in vials of 20 mL volume, wherein each vial contains about 1000-1060 mg of GM37v2, such as about 1060 mg.

Synucleinopathies and prodromal synucleinopathies

Synucleinopathies, refer to disorders characterized by the neural inclusion of pathologic alpha synuclein aggregates called Lewy bodies. Synucleinopathies include Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease) and Diffuse Lewy Body (DLB) disease (also known as Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson disease (CAPD), pure autonomic failure (PAF) and multiple system atrophy (MSA; e.g., Olivopontocerebellar Atrophy, Striatonigral Degeneration and Shy-Drager Syndrome)). In one aspect the present invention provides suitable dosage regimens for treating synucleinopathies, such as Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA). In preferred embodiments the synucleinopathy is PD. In another preferred embodiment the synucleinopathy is DLB. In yet another preferred embodiment the synucleinopathy is MSA.

In yet another preferred embodiment, the human subject suffering from MSA has MSA-C. In yet another embodiment, the human subject suffering from MSA has MSA-P. In yet another preferred embodiment, the human subject suffering from MSA has possible or probable MSA-C. In yet another embodiment, the human subject suffering from MSA has possible or probable MSA-P.

In yet another preferred embodiment, the human subject suffering from MSA has MSA in the early disease stage. In yet another such embodiment, the human subject suffering from MSA has MSA in an early disease stage. In yet another such embodiment, the human subject suffering from MSA has early MSA. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at the first administration with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In yet another preferred embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15. In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody. In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40,

such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug). In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at the first administration with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In another aspect the present invention provides suitable dosage regimens for treating prodromal synucleinopathies in a human subject in risk of developing synucleinopathy being identifiable by exhibiting one or more clinical markers of prodromal synucleinopathies. Such clinical markers of prodromal synucleinopathies may be selected from REM Sleep Behaviour Disorder (RBD) such as isolated RBD (iRBD), dysfunctional olfaction such as hyposmia, abnormal cognitive performance in neuropsychological testing, subtle motor dysfunction or abnormal motor performance assessed by objective testing, abnormal color vision, autonomic dysfunctions (such as constipation, urinary symptoms, erectile dysfunction, orthostatic hypotension), reduced nigrostriatal dopaminergic binding in the putamen and striatum (abnormal DAT-SPECT), Seborrhoeic dermatitis, and a genotype associated with increasing phenoconversion risk such as mutations in glucocerebrosidase (encoded by the GBA gene).

In some embodiments of these aspects, the human subject is identified as having signs of synucleinopathies or prodromal synucleinopathies in the form of abnormal accumulation or deposition of alpha synuclein in the central nervous system. In certain embodiments, the human subject is identified by in vivo imaging of alpha synuclein (e.g. in the brain) by a method comprising positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging, magnetic resonance imaging (MRI), dopamine transporter (DAT) imaging, or substantia nigra ultrasonography.

In some embodiments, the human subject is identified as having signs of synucleinopathies or prodromal synucleinopathies by assaying the level of alpha synuclein in a blood, plasma, or cerebrospinal fluid (CSF) sample obtained from the subject and comparing the assayed

level of alpha synuclein in the subject to a reference standard, wherein the difference or similarity between the level of alpha synuclein in the blood, plasma, or CSF sample and the reference standard correlates with the level of alpha synuclein in the brain of the subject. The level of alpha synuclein may be assessed by methods known in the art comprising, e.g., analyzing alpha synuclein by one or more techniques chosen from Western blot, immunoprecipitation, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), fluorescent activated cell sorting (FACS), two-dimensional gel electrophoresis, mass spectroscopy (MS), matrix-assisted laser desorption/ionization-time of flight-MS (MALDI-TOF), surface-enhanced laser desorption ionization-time of flight (SELDI-TOF), high performance liquid chromatography (HPLC), fast protein liquid chromatography (FPLC), multidimensional liquid chromatography (LC) followed by tandem mass spectrometry (MS/MS), and laser densitometry.

In some embodiments the human subject has been identified by having symptoms of synucleinopathies or prodromal synucleinopathies via acknowledged methods and criteria in the field.

Recently new diagnostic criteria for MSA “The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy” was published by Wenning et al. which is hereby incorporated by reference (Wenning et al., Movement Disorders, 2022, Volume 37, Issue 6, Pages 1131-1148). These new criteria describe “Research criteria for possible prodromal MSA” which may be used to identify a patient with prodromal synucleinopathy:

Essential features	A sporadic, progressive adult (>30 years) onset disease
Clinical non-motor features (entry criteria)	At least one of the following: • RBD (polysomnography proven) • Neurogenic OH (≥20/10 mmHg blood pressure drop) within 10 minutes of standing or head-up tilt • Urogenital failure (erectile dysfunction in males below age of 60 years combined with at least one of unexplained voiding difficulties with post-void urinary residual volume >100 mL and unexplained urinary urge incontinence)
Clinical motor features	At least one of the following: • Subtle parkinsonian signs • Subtle cerebellar signs
Exclusion criteria	Absence
Exclusion criteria	
At least one of unexplained anosmia on olfactory testing or abnormal cardiac sympathetic imaging (^{123}I-MIBG-scintigraphy)	
Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities	
Recurrent visual hallucinations not induced by drugs within 3 years of disease onset	
Dementia according to DSM-V within 3 years of disease onset	
Downgaze supranuclear gaze palsy or slowing of vertical saccades	
Brain MRI findings suggestive of an alternative diagnosis (eg, PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.)	
Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient's symptoms	

Abbreviations: MSA, multiple system atrophy; RBD, rapid eye movement sleep behavior disorder; OH, orthostatic hypotension; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; MRI, magnetic resonance imaging; PSP, progressive supranuclear palsy.

Parkinson's Disease (PD)

Parkinson's Disease (PD) is a synucleinopathy disorder. There are no well-defined diagnostic criteria for PD, however, there are various symptoms and diagnostic tests that can be used in

combination to support a PD diagnosis. Making an accurate diagnosis of Parkinson's, particularly in its early stages, is difficult, but a skilled practitioner can come to a reasoned conclusion that the human subject suffers from PD by using clinical assesment tools. In some embodiments the PD diagnosis may be based on the presence of at least two of the four main symptoms of PD:

a) Shaking or tremor
b) Slowness of movement, called bradykinesia
c) Stiffness or rigidity of the arms, legs or trunk
d) Trouble with balance and possible falls, also called postural instability.

Imaging techniques such as MRI, ultrasound of the brain, PET scans, and/or specific single-photon emission computerized tomography (SPECT) scan e.g. to analyse dopamine transport (DaTscan) may also be useful in supporting the diagnosis of PD.

Dementia with Lewy Bodies (DLB)

Dementia with Lewy bodies is a type of synucleinopathy that involves progressive dementia that leads to a decline in thinking, reasoning and independent function. Dementia with Lewy bodies is often hard to diagnose because its early symptoms may resemble those of Alzheimer's disease or a psychiatric illness. There are no definitive diagnostic criteria but some core clinical symptoms of DLB are Dementia, Movement problems/parkinsonism, Cognitive fluctuations, Visual hallucinations and REM sleep behavior disorder. Some supportive clinical symptoms are Extreme sensitivity to antipsychotic medications, Falls or fainting, Severe problems with involuntary functions (maintaining blood pressure, incontinence, constipation, loss of smell), Changes in personality and mood (depression, apathy, anxiety).

A diagnosis of Lewy body dementia requires a progressive decline in ability to think, as well as at least two of the following:

a) Fluctuating alertness and thinking function
b) Repeated visual hallucinations
c) Parkinsonian symptoms
d) REM sleep behaviour disorder

Autonomic dysfunction, which involves instability in blood pressure and heart rate, poor regulation of body temperature, sweating, and related signs and symptoms, further supports a Lewy body dementia diagnosis, and so does sensitivity to antipsychotic drugs.

Physical and neurological examinations and various tests can help distinguish DLB from other illnesses and support the diagnosis of DLB. Such specific test can be positron emission tomography (PET) scan or a single-photon emission computerized tomography (SPECT) scan showing reduced dopamine transporter (DAT) uptake in the basal ganglia (brain region), Abnormal ^{123}iodine-MIBG myocardial scintigraphy showing reduced communication of cardiac nerves or Sleep study confirming REM sleep behaviour disorder without loss of muscle tone.

Multiple System Atrophy (MSA)

Multiple system atrophy (MSA) is the most rapidly progressive of the synucleinopathies, a group of disorders characterized by the abnormal deposition of the protein alpha synuclein in the central and peripheral autonomic nervous system. In the present context the term MSA is meant to refer to all types of MSA such as the multiple system atrophy parkinsonian type (MSA-P) or multiple system atrophy cerebellar type (MSA-C). MSA is sometimes denoted as Olivopontocerebellar Atrophy, progressive autonomic failure with multiple system atrophy, Striatonigral Degeneration or Shy-Drager Syndrome. The present invention also provides dosage regimens for the treatment of MSA in all stages of disease progression including prodromal, early, moderate and advanced stages and all stages between.

Diagnosing multiple system atrophy (MSA) can be challenging as certain signs and symptoms of MSA, such as muscle rigidity and unsteady gait, also occur with other disorders, such as Parkinson's disease. A proper clinical examination, with various autonomic tests and imaging studies, may assist in determining whether the diagnosis is probable MSA or possible MSA. Examples of clinical methods which can be useful in supporting the MSA diagnosis of patients with suspected MSA is structural and functional brain imaging, cardiac sympathetic imaging, cardiovascular autonomic testing, olfactory testing, sleep study, urological evaluation, and dysphagia, cognitive assessments, skin biopsy, retinal biomarkers, blood and/or cerebrospinal fluid biomarkers, and genetic testing. Diagnosis of possible or probable MSA can for example be facilitated by the so-called Gilman criteria (Gilman et al., Neurology. 2008 Aug 26; 71(9): 670–676).

In some embodiments the human subject to be treated has probable MSA, which may be identifiable by:

a) Autonomic failure involving urinary incontinence or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic; and

b) Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor or postural instability); or

c) A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia or cerebellar oculomotor dysfunction).

In some embodiments the human subject to be treated has possible MSA, which may be identifiable by:

a) Parkinsonism (bradykinesia with rigidity tremor or postural instability); or

b) Cerebellar syndrome (gait ataxia with cerebellar dysarthria limb ataxia or cerebellar oculomotor dysfunction); and

c) At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency frequency or incomplete bladder emptying erectile dysfunction in males or significant orthostatic blood pressure decline that does not meet the level required in probable MSA); and

d) At least one of the following features:

For possible MSA-P or MSA-C:

i. Babinski sign with hyperreflexia

ii. Stridor

For possible MSA-P:

iii. Rapidly progressive parkinsonism

iv. Poor response to levodopa

v. Postural instability within 3 years of motor onset

vi. Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction

vii. Dysphagia within 5 year of motor onset

viii. Atrophy on MRI of putamen middle cerebellar peduncle, pons or cerebellum

ix. Hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) in putamen, brainstem or cerebellum

For possible MSA-C:

x. Parkinsonism (bradykinesia and rigidity)

xi. Atrophy on MRI of putamen, middle cerebellar peduncle, or pons

xii. Hypometabolism on FDG-PET in putamen

xiii. Presynaptic nigrostriatal dopaminergic denervation on single photon emission computed tomography (SPECT) or PET.

Currently, a definite MSA diagnosis can only be confirmed post-mortem by examination of:

a) Widespread and abundant cerebral alpha synuclein–positive glial cytoplasmic inclusions; and/or

b) Neurodegenerative changes in striatonigral or olivopontocerebellar region.

In a preferred embodiment, the human subject suffering from MSA also has MSA-C.

In a preferred embodiment, the human subject suffering from MSA also has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at the first administration with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In a preferred embodiment, the human subject suffering from MSA also has having an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In a preferred embodiment, the human subject suffering from MSA also has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at the first administration with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In a preferred embodiment, the human subject suffering from MSA also has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

Recently new diagnostic criteria for MSA "The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy" was published by Wenning et al. (Wenning et al., Movement Disorders, 2022, Volume 37, Issue 6, Pages 1131-1148).

These criteria include diagnosis of clinically established MSA and clinically probable MSA:

Division into clinically established MSA-P or MSA-C according to predominant motor syndrome			
Essential features	A sporadic, progressive adult (>30 years) onset disease		
	Clinically established MSA	**Clinically probable MSA**	
Core clinical features	1. Autonomic dysfunction defined as (at least one is required) ○ Unexplained voiding difficulties with post-void urinary residual volume ≥100 mL ○ Unexplained urinary urge incontinence ○ Neurogenic OH (≥20/10 mmHg blood pressure drop) within 3 minutes of standing or head-up tilt test and at least one of 1. Poorly L-dopa-responsive parkinsonism 2. Cerebellar syndrome (at least two of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)	At least two of: 1. Autonomic dysfunction defined as (at least one is required): ○ Unexplained voiding difficulties with post-void urinary residual volume ○ Unexplained urinary urge incontinence ○ Neurogenic OH (≥20/10 mmHg blood pressure drop) within 10 minutes of standing or head-up tilt test 2. Parkinsonism 3. Cerebellar syndrome (at least one of gait ataxia, limb ataxia, cerebellar dysarthria, or oculomotor features)	
Supportive clinical (motor or non-motor) features	At least two	At least one*	
MRI marker	At least one	Not required	
Exclusion criteria	Absence	Absence	
Supportive clinical features			
Supportive motor features	Rapid progression within 3 years of motor onset	**Supportive non-motor features**	Stridor
	Moderate to severe postural instability within 3 years of motor onset		Inspiratory sighs
	Craniocervical dystonia induced or exacerbated by L-dopa in the absence of limb dyskinesia		Cold discolored hands and feet
	Severe speech impairment within 3 years of motor onset		Erectile dysfunction (below age of 60 years for clinically probable MSA)
	Severe dysphagia within 3 years of motor onset		Pathologic laughter or crying
	Unexplained Babinski sign		
	Jerky myoclonic postural or kinetic tremor		
	Postural deformities		

MRI markers of clinically established MSA	
Each affected brain region as evidenced by either atrophy or increased diffusivity counts as one MRI marker.	
For MSA-P	For MSA-C
• Atrophy of: ○ Putamen (and signal decrease on iron-sensitive sequences) ○ Middle cerebellar peduncle ○ pons ○ Cerebellum • "Hot cross bun" sign	• Atrophy of: ○ Putamen (and signal decrease on iron-sensitive sequences) ○ Infratentorial structures (pons and middle cerebellar peduncle) • "Hot cross bun" sign
• Increased diffusivity of: ○ Putamen ○ Middle cerebellar peduncle	• Increased diffusivity of: ○ Putamen
Exclusion criteria	
Substantial and persistent beneficial response to dopaminergic medications	
Unexplained anosmia on olfactory testing	
Fluctuating cognition with pronounced variation in attention and alertness and early decline in visuoperceptual abilities	
Recurrent visual hallucinations not induced by drugs within 3 years of disease onset	
Dementia according to DSM-V within 3 years of disease onset	
Downgaze supranuclear palsy or slowing of vertical saccades	
Brain MRI findings suggestive of an alternative diagnosis (eg, PSP, multiple sclerosis, vascular parkinsonism, symptomatic cerebellar disease, etc.)	
Documentation of an alternative condition (MSA look-alike, including genetic or symptomatic ataxia and parkinsonism) known to produce autonomic failure, ataxia, or parkinsonism and plausibly connected to the patient's symptoms	

[a]Excluding erectile dysfunction as an isolated feature.
Abbreviations: MSA, multiple system atrophy; MSA-P, MSA-parkinsonian type; MSA-C, MSA-cerebellar type; OH, orthostatic hypotension; MRI, magnetic resonance imaging; DSM-V, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PSP, progressive supranuclear palsy.

MSA-C is characterized by predominant cerebellar symptoms. These cerebellar dysfunction symptoms often manifest as gait ataxia, limb ataxia, ataxic dysarthria, and/or eye movement abnormalities such as dysmetria, saccadic intrusion, and/or ocular dysmetria.

MSA-P is characterized by predominant parkinsonian features. These features comprise bradykinesia, rigidity, irregular jerky postural tremor and/or abnormal postures (camptocormia, Pisa syndrome and disproportionate antecollis).

Early MSA is meant to refer to patients who are less impaired in their disease stage. Such MSA patients will in the present context have a low score on any of the UMSARS scales, such as the mUMSARS, aUMSARS, UMSARS TS, UMSARS Part I or UMSARS Part II. In preferred embodiments early MSA means that the patient has an UMSARS TS of below 40 at the treatment initiation, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15.

REM Sleep Behaviour Disorder (RBD)

Rapid eye movement (REM) sleep behavioral disorder (RBD) is considered to be an early manifestation of synucleinopathy. REM Sleep Behavior Disorder (RBD) is characterized by "acting out" of dreams and is diagnosed by video-polysomnography (vPSG) demonstrating a loss of muscle atonia that normally accompanies REM sleep. REM Sleep Behavior Disorder (RBD), such as clinically Isolated RBD (iRBD) (previously sometimes referred to as idiopathic RBD), is the most reliable clinical marker of prodromal synucleinopathies, a group of neurodegenerative disorders including Parkinson's disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA). The vast majority of individuals with REM Sleep Behavior Disorder (RBD), such as iRBD are diagnosed with a synucleinopathy within 20 years of onset of iRBD, such as within 3 years, within 5 years, within 8 years or within 16 years. Therefore, the REM Sleep Behavior Disorder (RBD) populations can serve as an ideal group for administering the antibodies for use according to the invention to modify synuclein-specific neurodegeneration progression, i.e. to obtain a disease-modifying treatment that delays or prevent phenoconversion to an overt synucleinopathy.

RBD diagnosis may be based on certain consensus criteria, such as the ones established by the International Classification of Sleep Disorders (ICSD-3), or the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V), or the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events. A confirmatory RBD diagnosis may require confirmation by vPSG analysis. RBD diagnosis may be further supported by assessment using varoius imaging techniques which are also useful to identify synucleinopathies such as positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging, magnetic resonance imaging (MRI), dopamine transporter (DAT) imaging, or substantia nigra ultrasonography.

Unified Multiple System Atrophy Rating Scale (UMSARS)

The UMSARS is a well-known combined clinician and patient/caregiver-reported scale to assess disease progression in patients with MSA. The UMSARS scale can be used in clinical settings to assess MSA patients both for monitoring disease progression and/or to quantify treatment response.

The UMSARS consists of four parts:

Part I assesses historical information on symptoms and activities of daily living over the past two weeks as reported by patients and caregivers (12 items) rated on a scale ranging from 0

= not affected to 4 = unable to do the activity (Note; each item uses different anchor descriptors as relevant to the question addressed).

Part II consist of a clinical examination of key MSA motor signs and symptoms (14 items) rated on a scale ranging from 0 = normal to 4 = marked/severe impairment (Note; each item uses different anchor descriptors as relevant to the question addressed).

Part III includes an autonomic examination (4 items), individual measures of systolic and diastolic blood pressure, heart rate and orthostatic symptoms (yes/no).

Part IV assess global disability (1 item) ranging on a scale from 1 = completely independent to 5 = totally dependent and helpless/bedridden.

The total UMSARS score (UMSARS TS) is obtained by the sum of the items from Part I and Part II. Part I scores range between 0 to 48, and Part II scores range between 0 and 56. A higher score indicates greater impairment. An experienced neurologist can use the UMSARS after a short training session.

The modified UMSARS (mUMSARS) score in the present context consist of UMSARS Part 1 where the response option scores of 0 and 1 will be collapsed to one category in the analysis.

The abbreviated UMSARS (aUMSARS) score can be derived from a subset of items from UMSARS Part I and Part II shown to be patient centric and sensitive to progression in MSA. Abbreviated UMSARSs can be developed to be patient centric (relevant to patients) and sensitive to detect change in patients diagnosed with possible MSA, probable MSA, clinically established MSA or clinically probable MSA. The abbreviated UMSARS score is based on a subset of items from Part I and Part II in the original UMSARS scale. The items to be included in the aUMSARS score can for example be identified by 1) Finding items that are sensitive to change based on slopes and/or Patient centric/focused based on correlations with QoL scales, 2) Combining them into an abbreviated version of the UMSARS; i.e by excluding items with low patient centricity/focus and with low ability to detect change over time. Data used to develop the aUMSARS can for example be taken from the European MSA study group natural history study and the MSA-Ras trial. Sensitivity of change of a sub-item of the Unified MSA Rating Scale can be assessed by calculation of a sensitivity to change ratio using its mean slope of progression divided by the standard deviation of the slope when modelling its progression over time with a Linear Mixed Model. Patient-centricity can be assessed on the basis of correlation of Unified MSA Rating Scale items with quality of life measures.

An example of such aUMSARS is presented below and this specific aUMSARS include the following 19 Part I and Part II UMSARS items:

Part 1	
Swallowing	P1 Q2
Handwriting	P1 Q3
Dressing	P1 Q5
Hygiene	P1 Q6
Walking	P1 Q7
Orthostatic symptoms	P1 Q9
Urinary symptoms	P1 Q10
Bowel function	P1 Q12
Part 2	
Facial expression	P2 Q1
Ocular motor dysfunction	P2 Q3
Action tremor	P2 Q5
Increased tone	P2 Q6
Rapid alternating movement hands	P2 Q7
Finger taps	P2 Q8
Leg agility	P2 Q9
Heel-knee-shin test	P2 Q10
Arising from chair	P2 Q11
Posture	P2 Q12
Gait	P2 Q14

SPECIFIC EMBODIMENTS

The following embodiments describes the invention in further detail.

In one embodiment the invention provides a monoclonal alpha synuclein antibody for use in the treatment of synucleinopathies or prodromal synucleinopathies, wherein the use comprises administering a monoclonal alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein the monoclonal alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one embodiment the invention provides a monoclonal alpha synuclein antibody for use in the treatment of synucleinopathies, wherein the use comprises administering a monoclonal alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg,

such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein the monoclonal alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one embodiment the invention provides a monoclonal alpha synuclein antibody for use in the treatment of prodromal synucleinopathies, wherein the use comprises administering a monoclonal alpha synuclein antibody intravenously to a human subject suffering from synucleinopathy or in risk of developing synucleinopathy, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, or such as between 1000 mg to 4500 mg, and wherein the monoclonal alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one embodiment the invention provides a monoclonal alpha synuclein antibody for use in the treatment of MSA, wherein the use comprises administering a monoclonal alpha synuclein antibody intravenously to a human subject suffering from MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 4000 mg to 7000 mg, or such as between 1000 mg to 4500 mg, and wherein the monoclonal alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one embodiment the invention provides a monoclonal alpha synuclein antibody for use in the treatment of MSA, wherein the use comprises administering a monoclonal alpha synuclein antibody intravenously to a human subject suffering from MSA, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 4000 mg to 7000 mg, or such as between 1000 mg to 4500 mg, and wherein the monoclonal alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In one embodiment the invention provides a monoclonal alpha synuclein antibody for use in the treatment of early MSA, wherein the use comprises administering a monoclonal alpha synuclein antibody intravenously to a human subject suffering from MSA in an early clinical stage, at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 4000 mg to 7000 mg, or such as between 1000 mg to 4500 mg,

and wherein the monoclonal alpha synuclein antibody is a full-length antibody that binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

In certain embodiments the monoclonal anti-alpha synuclein antibody has an estimated KD value of binding to the oligomeric form of alpha synuclein of about 0.5 nM.

In a further embodiment the monoclonal alpha synuclein antibody has a KD value of binding to the monomer form of alpha synuclein of about 36 nM.

In a further embodiment the monoclonal alpha synuclein antibody has a KD value of binding to the monomeric form of alpha synuclein of about 36 nM, and an estimated KD value of binding to the oligomeric form of alpha synuclein of about 0.5 nM.

In one embodiment, the ratio between the monomeric and oligomeric binding values is approximately 65-fold enhanced to the oligomeric form as compared to the monomeric form.

In a further embodiment the monoclonal alpha synuclein antibody has a human T½ of about 25-35 days, such as about 4 weeks, such as about 27-33 days, such as 28-32 days, such as 28-30 days, such as 28 days, such as 29 days, such as 30 days.

In a further embodiment the monoclonal alpha synuclein antibody has a KD value of binding to the monomer form of alpha synuclein of about 36 nM, and an estimated KD value of binding to the oligomeric form of alpha synuclein of 0.5 nM, such that the ratio between the monomeric and oligomeric binding is approximately 65 fold enhancement.

In a further embodiment the monoclonal alpha synuclein antibody has a KD value of binding to the monomer form of alpha synuclein of about 36 nM, and an estimated Kd value of binding to the oligomeric form of alpha synuclein of 0.5 nM, such that the ratio between the monomeric and oligomeric binding is approximately 65 fold enhancement, and the antibody has a T½ of about 28-30 days, such as 29 days.

In a further embodiment the monoclonal alpha synuclein antibody 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**.

In a further embodiment the monoclonal alpha synuclein 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**.

In a further embodiment the monoclonal alpha synuclein antibody 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**;

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**.

In a further embodiment the monoclonal alpha synuclein 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**.

In a further embodiment the monoclonal alpha synuclein antibody 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**;

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**.

In a further embodiment the monoclonal alpha synuclein antibody comprises a heavy chain variable domain consisting of **SEQ ID NO:31** and a light chain variable domain consisting of **SEQ ID NO:8**.

In a further embodiment the monoclonal alpha synuclein antibody 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**;

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**.

In a further embodiment the monoclonal alpha synuclein antibody comprises a heavy chain consisting of a variable domain of **SEQ ID NO:32** and a light chain consisting of a variable domain of **SEQ ID NO:8**.

In a further embodiment the monoclonal alpha synuclein antibody is a full-length human antibody.

In a further embodiment the monoclonal alpha synuclein antibody is a human IgG1 antibody.

In a further embodiment the monoclonal alpha synuclein antibody is GM37.

In a further embodiment the monoclonal alpha synuclein antibody is GM37 variant 1.

In a further embodiment the monoclonal alpha synuclein antibody is GM37 variant 2.

In a further embodiment the monoclonal alpha synuclein antibody is GM37 variant 3.

In a further embodiment the monoclonal alpha synuclein antibody further comprises a constant heavy chain domain as defined in **SEQ ID NO:18** and a kappa light chain constant domain as defined in **SEQ ID NO:17**.

In a further embodiment the monoclonal alpha synuclein antibody is administered every 4 weeks or 28 days.

In a further embodiment the monoclonal alpha synuclein antibody is administered once monthly.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of more than 700 mg and less than 7000 mg, such as between 900 mg to 5000 mg, such as between 4000 mg to 7000 mg, or such as between 1000 mg to 4500 mg, at intervals of 3-5 weeks.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of 750 mg, 2250 mg, 4500 mg or 6300 mg.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of 1000 mg to 4500 mg, such as between 2000 mg to 4500 mg, such as between 4000 mg to 7000 mg, or between 3500 mg to 4500 mg.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of 750 mg, 1050 mg, 1400 mg, 1750 mg, 2100 mg, 2450 mg, 2800 mg, 3150 mg, 3500 mg, 3850 mg, 4200 mg, 4550 mg, 4900 mg, 5250 mg, 5600 mg, 5950 mg, 6300 mg, or 6650 mg.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of 1050 mg, 2100 mg, 4200 mg or 6300 mg.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose 4200 mg.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose 6300 mg.

In one embodiment, the dose is a fixed dose.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of 1050 mg, 2100 mg, 4200 mg or 6300 mg every 28-30 days.

In a further embodiment the monoclonal alpha synuclein antibody is administered at a dose of 4200 mg every 4 weeks or every 28-30 days, such as every 28 days, every 29 days or every 30 days.

In a further embodiment the monoclonal alpha synuclein antibody is administered by intravenous infusion over 30 minutes ±10 minutes.

In a further embodiment the monoclonal alpha synuclein antibody is administered by intravenous infusion over 15 minutes ±5 minutes.

In a further embodiment the monoclonal alpha synuclein antibody is administered by intravenous infusion at a speed of between 25 mg/min to 300 mg/min.

In a further embodiment the monoclonal alpha synuclein antibody is administered by intravenous infusion at a speed of between 30 mg/min to 150 mg/min, such as 35 mg/min, 70 mg/min or 140 mg/min.

In a further embodiment the monoclonal alpha synuclein antibody is administered by intravenous infusion at a speed of between 60 mg/min to 300 mg/min, such as 70 mg/min, 140 mg/min or 280 mg/min.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated CSF mean steady state concentration of the antibody of at least 0.5 nM, such as at least 1 nM, such as at least 2 nM, such as at least 3 nM, such as at least 6 nM, such as at least 12 nM, or such as 18 nM.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated CSF mean steady state concentration of the antibody of at least 3 nM.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated CSF mean steady state concentration of the antibody of at least 6 nM.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated CSF mean steady state concentration of the antibody of at least 12 nM.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated CSF mean steady state concentration of the antibody of at least 18 nM.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 50%, such as at least 60%, such as at least 75 %, such as at least 80 %, such as at least 85 %, such as at least 90 %, such as at least 95%, or such as at least 99 %.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 85 %.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 90 %.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 95 %.

In a further embodiment the monoclonal alpha synuclein antibody is administered in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 97 %.

In a further embodiment the synucleinopathy to be treated is selected from the list consisting of: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA).

In a further embodiment the synucleinopathy to be treated is selected from: Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), or multiple system atrophy (MSA).

In a further embodiment the synucleinopathy to be treated is multiple system atrophy (MSA) or a MSA subtype selected from: possible MSA, probable MSA, MSA type C, MSA type P, clinically established MSA or clinically probable MSA.

In a further embodiment the synucleinopathy to be treated is selected from: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA), and the treatment comprising administering to a patient the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve a CSF steady state concentration of the antibody of at least 0.5 nM, such as at least 1 nM, such as at least 2 nM, such as at least 3 nM, such as at least 6 nM, or such as at least 12 nM.

In a further embodiment the synucleinopathy to be treated is selected from: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers

Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA), and the treatment comprising administering to a patient the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve a CSF steady state concentration of the antibody of at least 3 nM, such as at least 6 nM, or such as at least 12 nM.

In a further embodiment the invention provides a method of treating a synucleinopathy selected from: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA), where the treatment comprising administering to a patient the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 50%, such as at least 60%, such as at least 75 %, such as at least 80 %, such as at least 85 %, such as at least 90 %, such as at least 95%, such as at least 97 %, or such as at least 99 %.

In a further embodiment the invention provides a method of treating a synucleinopathy selected from: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure and multiple system atrophy (MSA), where the treatment comprising administering to a patient the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 85 %, such as at least 90 %, such as at least 95% or such as at least 97 %.

In a further embodiment the invention provides a method of treating a synucleinopathy selected from: Parkinson's disease (PD) (including idiopathic and inherited forms of Parkinson's disease), Gauchers Disease (GD), Diffuse Lewy Body Disease (DLBD), Dementia with Lewy Bodies (DLB), Lewy body variant of Alzheimer's disease (LBV), Combined Alzheimer's and Parkinson's disease, pure autonomic failure or multiple system atrophy (MSA).

In a further embodiment the invention provides a method of treating a synucleinopathy selected from: Parkinson's disease (PD), Dementia with Lewy Bodies (DLB), or multiple system atrophy (MSA).

In a further embodiment the invention provides a method of treating a synucleinopathy which is multiple system atrophy (MSA) such as a MSA subtype selected from: possible MSA, probable MSA, MSA type C, MSA type P, clinically established MSA or clinically probable MSA.

In a further embodiment the invention provides a monoclonal alpha synuclein antibody, for treating a human subject suffering from multiple system atrophy (MSA) of the multiple system atrophy parkinsonian type (MSA-P) or multiple system atrophy cerebellar type (MSA-C) subtype.

In a further embodiment the invention provides a monoclonal alpha synuclein antibody, treating a human subject suffering from multiple system atrophy (MSA), which is identifiable by having had onset of motor and/or autonomic (orthostatic or urinary) MSA symptoms within the last 5 years, such as within the last 4 years, or such as within the last 3 years, or such as within the last 2 years, or such as within the last year.

In a further embodiment the invention provides a monoclonal alpha synuclein antibody, for treating a human subject suffering from multiple system atrophy (MSA), which is identifiable by having an UMSARS Part I score ≤16 (omitting question 11 on sexual function).

In a further embodiment the invention provides a monoclonal alpha synuclein antibody, for treating a human subject suffering from multiple system atrophy (MSA), which is identifiable by having a cognitive performance evaluated by the Montreal Cognitive Assessment (MoCA) with a score ≥22.

In yet another preferred embodiment, the human subject suffering from MSA has MSA-C. In yet another embodiment, the human subject suffering from MSA has MSA-P. In yet another preferred embodiment, the human subject suffering from MSA has possible or probable MSA-C. In yet another embodiment, the human subject suffering from MSA has possible or probable MSA-P.

In yet another preferred embodiment, the human subject suffering from MSA has MSA in the early disease stage. In yet another such embodiment, the human subject suffering from MSA has MSA in an early disease stage. In yet another such embodiment, the human subject suffering from MSA has early MSA. In yet another such embodiment, the human subject

suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody. In yet another such embodiment, the human subject suffering from MSA has an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at the first infusion with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In yet another preferred embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15. In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody. In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at treatment initiation with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug). In yet another such embodiment, the human subject suffering from MSA has MSA-C and an UMSARS TS of < 40, such as below 39, below 38, below 37, below 36, below 35, below 34, below 33, below 32, below 31, below 30, 10-39, 15-39, 20-39, 25-39, 30-39, 35-39, 10-35, 15-35, 20-35, 25-35, 30-35, 10-30, 15-30, 20-30, 25-30, 10-25, 15-25, 20-25, 10-20, 15-20, or 10-15 at the first infusion with the anti-alpha synuclein antibody, such as GM37v2 (Amlenetug).

In an embodiment the treatment of synucleinopathy consists of delaying or slowing disease progression.

In an embodiment the treatment of synucleinopathy consists of delaying or slowing clinical progression.

In an embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in any of the relevant Unified Multiple System Atrophy Rating Scale (UMSARS) scores described herein or any relevant parts of these scales, such as Part I, Part II, Part III or Part IV or a change from baseline in any combination of these parts of the UMSARS.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I and/or Part II or in the modified UMSARS Part I (mUMSARS) or in the abbreviated UMSARS (aUMSARS) scores.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I or Part II scores.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I and Part II scores.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I, modified UMSARS Part I (mUMSARS) and/or UMSARS Part II scores.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in UMSARS TS, UMSARS Part I, mUMSARS and/or UMSARS Part II scores.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in an abbreviated UMSARS (aUMSARS) score.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in the modified UMSARS (mUMSARS) score.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in the total Unified Multiple System Atrophy Rating Scale (UMSARS TS) score.

In a further embodiment the delay or slowing in disease or clinical progression is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI).

In a further embodiment the delay or slowing of disease progression of MSA is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the pons.

In a further embodiment the delay or slowing of disease progression of MSA is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum white matter.

In a further embodiment the delay or slowing of disease progression of MSA is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum gray matter.

In a further embodiment the delay or slowing of clinical progression of MSA is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the pons.

In a further embodiment the delay or slowing of clinical progression of MSA is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum white matter.

In a further embodiment the delay or slowing of clinical progression of MSA is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum gray matter.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 10%, e.g., at least 15%, at least 20%, at least 30%, at least 35%, 10-35%, 15-35%, 19-35%, 20-35%, 25-35%, 30-35%, 10-30%, 15-30%, 19-30%, 20-30%, 25-30%, 10-25%, 15-25%, 19-25%, 20-25%, 10-20%, 15-20%, 19-20%, or 10-15%, slowing of clinical progression in MSA measured with the UMSARS Total score. In a further embodiment

the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 19% slowing of clinical progression in MSA measured with the UMSARS Total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 10-35%, 15-35%, 19-35%, 20-35%, 25-35%, 30-35%, 10-30%, 15-30%, 19-30%, 20-30%, 25-30%, 10-25%, 15-25%, 19-25%, 20-25%, 10-20%, 15-20%, 19-20%, or 10-15% slowing of clinical progression in MSA measured with the UMSARS Total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 19% slowing of clinical progression in MSA measured with the UMSARS Total score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 10%, e.g., at least 15%, at least 20%, at least 30%, at least 35%, 10-35%, 15-35%, 20-35%, 22-35%, 25-35%, 30-35%, 10-30%, 15-30%, 20-30%, 22-30%, 25-30%, 10-25%, 15-25%, 20-25%, 22-25%, 10-20%, 15-20%, or 10-15%, slowing of clinical progression in MSA measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 22% slowing of clinical progression in MSA measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 10-35%, 15-35%, 20-35%, 22-35%, 25-35%, 30-35%, 10-30%, 15-30%, 20-30%, 22-30%, 25-30%, 10-25%, 15-25%, 20-25%, 22-25%, 10-20%, 15-20%, or 10-15% slowing of clinical progression in MSA measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 22% slowing of clinical progression in MSA measured with the UMSARS Part I score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 10%, e.g., at least 15%, at least 20%, at least 30%, at least 35%, 10-35%, 15-35%, 17-35%, 20-35%, 25-35%, 30-35%, 10-30%, 15-30%, 17-30%, 20-30%, 25-30%, 10-25%, 15-25%, 17-25%, 20-25%, 10-20%, 15-20%, 17-20%, or 10-15%, slowing of clinical progression in MSA measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 17% slowing of clinical progression in MSA measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug)

dosed every 4 weeks or once monthly is about a 10-35%, 15-35%, 17-35%, 20-35%, 25-35%, 30-35%, 10-30%, 15-30%, 17-30%, 20-30%, 25-30%, 10-25%, 15-25%, 17-25%, 20-25%, 10-20%, 15-20%, 17-20%, or 10-15% slowing of clinical progression in MSA measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 17% slowing of clinical progression in MSA measured with the UMSARS Part II score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 10%, e.g., at least 15%, at least 20%, at least 30%, at least 35%, 10-35%, 15-35%, 20-35%, 25-35%, 27-35%, 30-35%, 10-30%, 15-30%, 20-30%, 25-30%, 27-30%, 10-25%, 15-25%, 20-25%, 10-20%, 15-20%, or 10-15%, slowing of clinical progression in MSA measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least a 27% slowing of clinical progression in MSA measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 10-35%, 15-35%, 20-35%, 25-35%, 27-35%, 30-35%, 10-30%, 15-30%, 20-30%, 25-30%, 27-30%, 10-25%, 15-25%, 20-25%, 10-20%, 15-20%, or 10-15% slowing of clinical progression in MSA measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 27% slowing of clinical progression in MSA measured with the modified UMSARS score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 30%, e.g., at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 50-70%, 60-70%, 30-60%, 40-60%, 50-60%, 30-50%, 40-50%, or 30-40%, slowing of clinical progression in MSA-C measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 50% slowing of clinical progression in MSA-C measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-

90%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 50-70%, 60-70%, 30-60%, 40-60%, 50-60%, 30-50%, 40-50%, or 30-40% slowing of clinical progression in MSA-C measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 50% slowing of clinical progression in MSA-C measured with the modified UMSARS score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 30%, e.g., at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 50-70%, 60-70%, 30-60%, 40-60%, 50-60%, 30-50%, 40-50%, or 30-40%, slowing of clinical progression in MSA-C measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 50% slowing of clinical progression in MSA-C measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 50% slowing of clinical progression in MSA-C measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 50-70%, 60-70%, 30-60%, 40-60%, 50-60%, 30-50%, 40-50%, or 30-40% slowing of clinical progression in MSA-C measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 50% slowing of clinical progression in MSA-C measured with the UMSARS total score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 30%, e.g., at least 40%, at least 50%, at least 57%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 40-99%, 50-99%, 57-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 50-90%, 57-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 50-80%, 57-80%, 60-80%, 70-80%, 30-70%, 40-70%, 50-70%, 57-70%, 60-70%, 30-60%, 40-60%, 50-60%, 57-60%, 30-50%, 40-50%, or 30-40%, slowing of clinical progression in MSA-C measured with the UMSARS Part I score. In a further embodiment the

treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 57% slowing of clinical progression in MSA-C measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 40-99%, 50-99%, 57-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 50-90%, 57-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 50-80%, 57-80%, 60-80%, 70-80%, 30-70%, 40-70%, 50-70%, 57-70%, 60-70%, 30-60%, 40-60%, 50-60%, 57-60%, 30-50%, 40-50%, or 30-40% slowing of clinical progression in MSA-C measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 57% slowing of clinical progression in MSA-C measured with the UMSARS Part I score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 30%, e.g., at least 40%, at least 41%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 40-99%, 41-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 41-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 41-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 41-70%, 50-70%, 60-70%, 30-60%, 40-60%, 41-60%, 50-60%, 30-50%, 40-50%, 41-50%, or 30-40%, slowing of clinical progression in MSA-C measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about at least 41% slowing of clinical progression in MSA-C measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 40-99%, 41-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 41-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 41-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 41-70%, 50-70%, 60-70%, 30-60%, 40-60%, 41-60%, 50-60%, 30-50%, 40-50%, 41-50%, or 30-40% slowing of clinical progression in MSA-C measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 41% slowing of clinical progression in MSA-C measured with the UMSARS Part II score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in the pons by about a 0.8-1.5%, e.g., 1.0-1.5%, 1.2-1.5%, 0.8-1.2%, 1-1.2%, or 0.8-1.0%, less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or

once monthly in MSA-C is a slowing of regional volumetric reduction in the pons by about a 1.2% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by about a 2.5-5%, 3-5%, 3.5-5%, 4-5%, 2.5-4%, 3-4%, 3.5-4%, or 2.5-3%, less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by about a 3.8% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar gray matter by about a 0.2-0.6%, e.g., 0.3-0.6%, 0.4-0.6%, 0.5-0.6%, 0.3-0.5%, 0.4-0.5%, or 0.3-0.4%, less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar gray matter by about a 0.4% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in the pons by at least about a 0.8-1.5%, e.g., 1.0-1.5%, 1.2-1.5%, 0.8-1.2%, 1-1.2%, or 0.8-1.0%, less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in the pons by at least about a 1.2% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 2.5-5%, 3-5%, 3.5-5%, 4-5%, 2.5-4%, 3-4%, 3.5-4%, or 2.5-3%, less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.8% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar gray

matter by at least about a 0.2-0.6%, e.g., 0.3-0.6%, 0.4-0.6%, 0.5-0.6%, 0.3-0.5%, 0.4-0.5%, or 0.3-0.4%, less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least about a 30%, e.g., at least 40%, at least 42%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 40-99%, 42-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 42-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 42-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 42-70%, 50-70%, 60-70%, 30-60%, 40-60%, 42-60%, 50-60%, 30-50%, 40-50%, 42-50%, or 30-40%, slowing of clinical progression in early MSA measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least about a 42% slowing of clinical progression in early MSA measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 40-99%, 42-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 42-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 42-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 42-70%, 50-70%, 60-70%, 30-60%, 40-60%, 42-60%, 50-60%, 30-50%, 40-50%, 42-50%, or 30-40% slowing of clinical progression in early MSA measured with the modified UMSARS score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 42% slowing of clinical progression in early MSA measured with the modified UMSARS score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks is at least about a 30%, e.g., at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 37-99%, 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 37-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 37-80%, 40-80%, 50-80%, 60-80%, 70-80%, 30-70%, 37-80%, 40-70%, 50-70%, 60-70%, 30-60%, 37-60%, 40-60%, 50-60%, 30-50%, 37-50%, 40-50%, 37-40%, or 30-40%, slowing of clinical progression in early MSA measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least

about a 37% slowing of clinical progression in early MSA measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 37-99%, 40-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 37-90%, 40-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 37-80%, 40-80%, 50-80%, 60-80%, 70-80%, 30-70%, 37-80%, 40-70%, 50-70%, 60-70%, 30-60%, 37-60%, 40-60%, 50-60%, 30-50%, 37-50%, 40-50%, 37-40%, or 30-40% slowing of clinical progression in early MSA measured with the UMSARS total score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks is about a 37% slowing of clinical progression in early MSA measured with the UMSARS total score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least about a 30%, e.g., at least 40%, at least 42%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, 30-99%, 40-99%, 42-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 42-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 42-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 42-70%, 50-70%, 60-70%, 30-60%, 40-60%, 42-60%, 50-60%, 30-50%, 40-50%, 42-50%, or 30-40%, slowing of clinical progression in early MSA measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least about a 42% slowing of clinical progression in early MSA measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30-99%, 40-99%, 42-99%, 50-99%, 60-99%, 70-99%, 80-99%, 90-99%, 30-90%, 40-90%, 42-90%, 50-90%, 60-90%, 70-90%, 80-90%, 30-80%, 40-80%, 42-80%, 50-80%, 60-80%, 70-80%, 30-70%, 40-70%, 42-70%, 50-70%, 60-70%, 30-60%, 40-60%, 42-60%, 50-60%, 30-50%, 40-50%, 42-50%, or 30-40% slowing of clinical progression in early MSA measured with the UMSARS Part I score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 42% slowing of clinical progression in early MSA measured with the UMSARS Part I score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least about a 10%, e.g., at least 15%, at least 20%, at least 30%, at least 35%, at least 40%, at least 50%, 10-50%, 15-50%, 20-50%, 25-50%, 30-50%, 35-50%, 40-50%, 45-50%, 10-45%, 15-45%, 20-45%, 25-45%, 30-45%, 35-45%, 40-45%, 10-40%, 15-40%, 20-

40%, 25-40%, 30-40%, 35-40%, 10-35%, 15-35%, 20-35%, 25-35%, 30-35%, 10-30%, 15-30%, 20-30%, 25-30%, 10-25%, 15-25%, 20-25%, 10-20%, 15-20%, or 10-15%, slowing of clinical progression in early MSA measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is at least about a 30% slowing of clinical progression in early MSA measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 10-50%, 15-50%, 20-50%, 25-50%, 30-50%, 35-50%, 40-50%, 45-50%, 10-45%, 15-45%, 20-45%, 25-45%, 30-45%, 35-45%, 40-45%, 10-40%, 15-40%, 20-40%, 25-40%, 30-40%, 35-40%, 10-35%, 15-35%, 20-35%, 25-35%, 30-35%, 10-30%, 15-30%, 20-30%, 25-30%, 10-25%, 15-25%, 20-25%, 10-20%, 15-20%, or 10-15% slowing of clinical progression in early MSA measured with the UMSARS Part II score. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly is about a 30% slowing of clinical progression in early MSA measured with the UMSARS Part II score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in the pons by about a 1.8-3.0%, 2-2.8%, 2.2-2.6%, or 2.3-2.5% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in the pons by about a 2.4% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by about a 3-5%, 3.5-4.5%, 4-5%, or 4-4.5% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by about a 4.2% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by about a 0.2-0.6%, e.g., 0.3-0.6%, 0.4-0.6%, 0.5-0.6%, 0.3-0.5%, 0.4-0.5%, or 0.3-0.4%, less volume reduction. In a further embodiment the treatment effect of GM37v2

(Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by about a 0.4% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in the pons by at least about a 2.4% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in the pons by about a 1.8-3.0%, 2-2.8%, 2.2-2.6%, or 2.3-2.5% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 4.2% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by about a 3-5%, 3.5-4.5%, 4-5%, or 4-4.5% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.2-0.6%, e.g., 0.3-0.6%, 0.4-0.6%, 0.5-0.6%, 0.3-0.5%, 0.4-0.5%, or 0.3-0.4%, less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with the UMSARS Part IV - Global disability score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by about a 0.1-0.3, 0.2-0.3, or 0.1-0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by about a 0.2 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by about a 0.6-1.0, 0.7-1.0, 0.8-1.0, 0.6-0.9, 0.7-0.9, 0.6-0.8, or 0.7-0.8 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by about a 0.8 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.8 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by about a 0.6-1.0, 0.7-1.0, 0.8-1.0, 0.6-0.9, 0.7-0.9, 0.6-0.8, or 0.7-0.8 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score. In a further embodiment the treatment effect of

GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score.
In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks in or once monthly MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by about a 0.1-0.3, 0.2-0.3, or 0.1-0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by about a 0.2 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.5 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by about a 0.3-0.7, 0.3-0.6, 0.3-0.5, 0.4-0.7, 0.4-0.6, 0.5-0.7, or 0.5-0.6 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by about a 0.5 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in the pons by at least

about a 1.9% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in the pons by about a 1-3%, 1.5-3%, 1.9-3%, 2-3%, 1-2.5%, 1-2%, 1.5-2%, 1-1.9%, or 1.9-2.5% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in the pons by about a 1.9% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.3% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in cerebellar white matter by about a 2-5%, 2.5-5%, 3-5%, 3.3-5%, 2-4%, 2.5-4%, 3-4%, 3.3-4%, 2-3.5%, 2.5-3.5%, 3-3.5%, 2-3.3%, 2.5-3.3%, or 3-3.3% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in cerebellar white matter by about a 3.3% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 1.5% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in cerebellar gray matter by about a 1-3%, 1-2.5%, 1-2%, 1-1.5%, 1.5-3%, 1.5-2.5%, or 1.5-2% less volume reduction. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of regional volumetric reduction in cerebellar gray matter by about a 1.5% less volume reduction.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a greater lowering of neurofilament light chain load in CSF. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a lowering of neurofilament light chain load in CSF by at least about 16.3%. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a lowering of neurofilament light chain load in CSF by about 10-25%, 10-20%, 10-16.3%, 10-15%, 15-25%, 15-20%, 15-16.3%, 16.3-25%, or 16.3-20%. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a lowering of neurofilament light chain load in CSF by about 16.3%.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a lowering of neurofilament light chain load in CSF by at least about 14.4%. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a lowering of neurofilament light chain load in CSF by about 5-25%, 10-25%, 14.4-25%, 15-25%, 20-25%, 5-20%, 10-20%, 14.4-20%, 15-20%, 5-15%, 10-15%, or 5-10%. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a lowering of neurofilament light chain load in CSF by about 14.4%.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “speech”. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.4 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by about a 0.2-0.6, 0.3-0.6, 0.4-0.6, 0.5-0.6, 0.2-0.5, 0.3-0.5, 0.4-0.5, 0.2-0.4, 0.3-0.4, or 0.2-0.3 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by about a 0.4 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with UMSARS Part I single item “speech”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.8 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by about a 0.6-1.0, 0.7-1.0, 0.8-1.0, 0.6-0.9, 0.7-0.9, 0.6-0.8, or 0.7-0.8 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by about a 0.8 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils”. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.3 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by about a 0.2-0.4, 0.3-0.4, or 0.2-0.3 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by about a 0.3 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.7 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by about a 0.5-0.9, 0.6-0.9, 0.7-0.9, 0.5-0.8, 0.6-0.8, 0.7-0.8, 0.5-0.7, or 0.6-0.7 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by about a 0.7 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene”. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene” by at least about a 0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene” by about a 0.1-0.3, 0.2-0.3, or 0.1-0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene” by about a 0.2 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with UMSARS Part I single item “hygiene”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene”. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene” by at least about a 0.6 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene” by about a 0.4-0.8, 0.5-0.8, 0.6-0.8, 0.7-0.8, 0.4-0.7, 0.5-0.7, 0.6-0.7, 0.4-0.6, 0.5-0.6, or 0.4-0.5 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “hygiene” by about a 0.6 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “walking”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “walking” by at least about a 0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “walking” by about a 0.1-0.3, 0.2-0.3, or 0.1-0.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part I single item “walking” by about a 0.2 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with UMSARS Part I single item “walking”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “walking”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “walking” by at least about a 0.4 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “walking” by about a 0.2-0.6, 0.3-0.6, 0.4-0.6, 0.5-0.6, 0.2-0.5, 0.3-0.5, 0.4-0.5, 0.2-0.4, 0.3-0.4, or 0.2-0.3 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part I single item “walking” by about a 0.4 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by at least about a 0.3 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by about a 0.2-0.4, 0.3-0.4, or 0.2-0.3 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by about a 0.3 score reduced impairment.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in MSA-C is a slowing of impairment as measured with UMSARS Part II single item “arising from chair”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair”.

In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by at least about a 1.2 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by about a 1.0-1.4, 1.1-1.4, 1.2-1.4, 1.3-1.4, 1.0-1.3, 1.1-1.3, 1.2-1.3, 1.0-1.2, 1.1-1.2, or 1.0-1.1 score reduced impairment. In a further embodiment the treatment effect of GM37v2 (Amlenetug) dosed every 4 weeks or once monthly in early MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by about a 1.2 score reduced impairment.

In a further embodiment the treatment of synucleinopathy consists of delaying or slowing disease progression by at least 5%, such as at least 10%, such as at least 15%, such as at least 20%, such as at least 25%, such as at least 30%, such as at least 35%, such as at least 40%, such as at least 45%, such as at least 50%, such as at least 55%, such as at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%, such as at least 85% or such as at least 90%.

In a further embodiment the treatment of synucleinopathy consists of delaying disease progression by at least 25%, such as at least 30%, such as at least 35% or such as at least 40%.

In a further embodiment the treatment effect on synucleinopathy is observed following administration of at least 10 doses of GM37v2 (Amlenetug), such as at least 11 doses, such as at least 12 doses, such as at least 13 doses, such as at least 14 doses, such as at least 15 doses, such as at least 16 doses, such as at least 17 doses, such as at least 18 doses, such as at least 19 doses or such as at least 20 doses.

In a further embodiment the treatment effect on synucleinopathy is observed following treatment with GM37v2 (Amlenetug) for at least 24 weeks, such as at least 48 weeks, such as at least 72 weeks or such as at least 96 weeks.

In a further embodiment the treatment effect on synucleinopathy is observed following treatment with GM37v2 (Amlenetug) for at least 44 weeks or at least 48 weeks.

In a further embodiment the treatment effect of synucleinopathy is observed following administration of at least 10 doses of GM37v2 (Amlenetug), such as at least 11 doses or such as at least 12 doses.

In yet another such embodiment, the human subject suffering from MSA has MSA-C. In yet another such embodiment, the human subject suffering from MSA has MSA-P. In yet another such embodiment, the human subject suffering from MSA has possible or probable MSA-C. In yet another such embodiment, the human subject suffering from MSA has possible or probable MSA-P.

In a further embodiment the delay in disease progression is quantified by longitudinal changes from baseline in Neurofilament Light Chain (NfL) blood concentrations.

In a further embodiment the delay or slowing of disease progression in MSA is quantified by longitudinal changes from baseline in Neurofilament Light Chain (NfL) blood concentrations.

In a further embodiment the delay in disease progression is quantified by longitudinal changes from baseline in one or more parameter selected from: Schwab and England Activities of Daily Living (SE-ADL) Score; as change from baseline in Clinical Global Impression – Severity of Illness (CGI-S) Score; as change from baseline in Patient Global Impression – Severity of Illness (PGI-S) Score; as change from baseline in Observer-Reported Global Impression – Severity of Illness (OGI-S) Score; as change from baseline in Composite Autonomic Symptom Score Select Change (COMPASS Select Change) Score; as change from baseline in UMSARS Part IV Score; as change from baseline in Speech, Swallowing, Falls, and Walking, as assessed by the UMSARS Part I Item Scores; as change from baseline in Frequency, Cause, and Consequence of Falls, as assessed by the Fall Diary Periods; as change from baseline in EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Score; as change from baseline in Brain Volume, as Measured by Volumetric MRI (vMRI); as change from baseline in Tissue Integrity, as Measured by Diffusion-Tensor Imaging (DTI) MRI; as change from baseline in

Neurofilament Light Chain (NfL) blood concentrations; as change from baseline in heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III; as change from baseline in gait parameters or frequency of falls, as assessed by digital wearable sensor-based devices that are capable of tracking relevant gait parameters and/or registering falls; as change from baseline in cerebral blood flow, as measured by arterial spin labelling (ASL) MRI; as change from baseline in t-tau and NfL CSF concentrations; or as change from baseline in concentration of pathological species of α-synuclein in CSF.

In a further embodiment the human subject in risk of developing synucleinopathy or suffering from prodromal synucleinopathy is identifiable by exhibiting one or more clinical markers of prodromal synucleinopathies selected from the group comprising: REM Sleep Behaviour Disorder (RBD) such as isolated RBD (iRBD), dysfunctional olfaction such as hyposmia, abnormal cognitive performance in neuropsychological testing, subtle motor dysfunction or abnormal motor performance assessed by objective testing, abnormal color vision, autonomic dysfunctions (such as constipation, urinary symptoms, erectile dysfunction, orthostatic hypotension), reduced nigrostriatal dopaminergic binding in the putamen and striatum (abnormal DAT-SPECT), Seborrhoeic dermatitis, and a genotype associated with increasing phenoconversion risk such as mutations in glucocerebrosidase (encoded by the GBA gene).

In a further embodiment the human subject in risk of developing synucleinopathy or suffering from prodromal synucleinopathy is identifiable by exhibiting RBD such as isolated RBD (iRBD), and at least one additional clinical marker of prodromal synucleinopathies, such as hyposmia and/or abnormal DAT-SPECT.

In a further embodiment the treatment of prodromal synucleinopathy consists of delaying disease onset.

In a further embodiment the treatment of prodromal synucleinopathy consists of delaying disease onset or time of disease diagnosis by at least 5%, such as at least 10%, such as at least 15%, such as at least 20%, such as at least 25%, such as at least 30%, such as at least 35%, such as at least 40%, such as at least 45%, such as at least 50%, such as at least 55%, such as at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%, such as at least 85% or such as at least 90%.

In a further embodiment the treatment of prodromal synucleinopathy consists of delaying disease onset or time of disease diagnosis by at least 6 months, such as at least 8 months, such as at least 10 months, such as at least 12 months, such as at least 14 months, such as at least 16 months, such as at least 18 months, such as at least 20 months, such as at least 22 months, such as at least 24 months, such as at least 2 years, such as at least 3 years, such as at least 4 years, such as at least 5 years.

In a further embodiment the invention provides a method of treatment of prodromal synucleinopathy where the treatment comprises administering the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve a CSF steady state concentration of the antibody of at least 0.5 nM, such as at least 1 nM, such as at least 2 nM, such as at least 3 nM, such as at least 6 nM, or such as at least 12 nM.

In a further embodiment the invention provides a method of treatment of prodromal synucleinopathy where the treatment comprises administering the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve a CSF steady state concentration of the antibody of at least 3 nM, such as at least 6 nM, or such as at least 12 nM.

In a further embodiment the invention provides a method of treatment of prodromal synucleinopathy where the treatment comprises administering the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 50%, such as at least 60%, such as at least 75 %, such as at least 80 %, such as at least 85 %, such as at least 90 %, such as at least 95%, or such as at least 99 %.

In a further embodiment the invention provides a method of treatment of prodromal synucleinopathy where the treatment comprises administering the monoclonal alpha synuclein antibody in an amount and a frequency sufficient to achieve an estimated target engagement to oligomeric forms of alpha synuclein in CSF of at least 85 %, such as at least 90 %, or such as at least 95%.

In an aspect the present invention also provides use of a liquid pharmaceutical composition comprising a full length IgG1 monoclonal anti-alpha synuclein antibody in a concentration of 25-225 mg/mL, wherein said antibody 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**;

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**;

and wherein the composition further comprises histidine buffer, a pharmaceutically acceptable tonicity agent, a pharmaceutically acceptable surfactant and wherein the pH of the composition is between 5.5 to 6.5, this liquid pharmaceutical composition is suitable to be used to administer the monoclonal alpha synuclein antibody in any of the treatment, the methods of treatment of uses described in the aspects, embodiments or claims of this application.

In an embodiment the monoclonal antibody of the liquid pharmaceutical composition comprises a heavy chain variable domain consisting of **SEQ ID NO:31** and a light chain variable domain consisting of **SEQ ID NO:8**.

In an embodiment the monoclonal antibody of the liquid pharmaceutical composition is a human antibody.

In an embodiment the monoclonal antibody of the liquid pharmaceutical composition is a human IgG1 antibody.

In an embodiment the monoclonal antibody of the liquid pharmaceutical composition is GM37 variant 2.

In a further embodiment the monoclonal antibody of the liquid pharmaceutical composition comprises a constant heavy chain domain as defined in **SEQ ID NO:18** and a kappa light chain constant domain as defined in **SEQ ID NO:17**.

In an embodiment the tonicity agent of the liquid pharmaceutical composition is selected from Mannitol, Sorbitol, Lactose, Dextrose, Trehalose, Sodium Chloride (NaCl), Potassium Chloride (KCl), Glycerol or Glycerine.

In an embodiment the tonicity agent of the liquid pharmaceutical composition is Sodium Chloride (NaCl).

In an embodiment the tonicity agent of the liquid pharmaceutical composition is Sodium Chloride (NaCl) in a concentration of about 70-140 mM.

In an embodiment the tonicity agent of the liquid pharmaceutical composition is Sodium Chloride (NaCl) in a concentration of about 50-150 mM.

In an embodiment the tonicity agent of the liquid pharmaceutical composition is Sodium Chloride (NaCl) in a concentration of about 100 mM.

In an embodiment the surfactant of the liquid pharmaceutical composition is selected from Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Poloxamer 188 or Triton X-100.

In an embodiment the surfactant of the liquid pharmaceutical composition is Polysorbate 80 (Tween 80) in an amount between 0.02% to 0.05% (w/v).

In an embodiment the surfactant of the liquid pharmaceutical composition is Polysorbate 80 (Tween 80) in an amount of about 0.02% (w/v).

In an embodiment the tonicity agent of the liquid pharmaceutical composition is Sodium Chloride (NaCl) and the surfactant is Polysorbate 80 (Tween 80).

In an embodiment the concentration of the histidine buffer of the liquid pharmaceutical composition is between 25-40 mM.

In an embodiment the concentration of the histidine buffer of the liquid pharmaceutical composition is about 25 mM.

In an embodiment the pH of the liquid pharmaceutical composition is 6.0.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 30-225 mg/mL.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 30-200 mg/mL.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 30-150 mg/mL.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 30-100 mg/mL.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 45-55 mg/mL.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 50 mg/mL.

In an embodiment the monoclonal anti-alpha synuclein antibody concentration of the liquid pharmaceutical composition is about 53 mg/mL.

In an embodiment the liquid pharmaceutical composition of any of the proceeding embodiments further comprises at least one bulking agent selected from Sucrose, Trehalose, Glucose, Lactose, Sorbitol, Mannitol, Glycerol, Arginine, Aspartic Acid, Glutamic acid, Glutamate, Lysine, Glycine, Histidine, Methionine, Alanine, Gelatin, PVP, PLGA, PEG, dextran, cyclodextrin and derivatives, starch derivatives, HSA or BSA.

In an embodiment the bulking agent of the liquid pharmaceutical composition is Arginine, Glutamate, Sucrose, Glycine or Sorbitol in a concentration of 100-200 mM.

In an embodiment the bulking agent of the liquid pharmaceutical composition is Sucrose in a concentration of 100 mM.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl) and 0.02% polysorbate 80 (Tween 80) (w/v) at pH 6.0.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl), 0.02% polysorbate 80 (Tween 80) (w/v) and water at pH 6.0.

In an embodiment the liquid pharmaceutical composition comprises 53 ±5 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) at pH 6.0.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 ±5 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) and water at pH 6.0.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM

sodium chloride (NaCl) and 0.02% polysorbate 80 (Tween 80) (w/v) or having amounts of each constituent within +/- 10% of said values, and having a pH of 6.0 or within +/- 10% of said value.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl), 0.02% polysorbate 80 (Tween 80) (w/v) and water or having amounts of each constituent within +/- 10% of said values, and having a pH of 6.0 or within +/- 10% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) or having amounts of each constituent within +/- 10% of said values, and having a pH of 6.0 or within +/- 10% of said value.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) and water or having amounts of each constituent within +/- 10% of said values, and having a pH of 6.0 or within +/- 10% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl) and 0.02% polysorbate 80 (Tween 80) (w/v) or having amounts of each constituent within +/- 5% of said values, and having a pH of 6.0 or within +/- 5% of said value.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl), 0.02% polysorbate 80 (Tween 80) (w/v) and water or having amounts of each constituent within +/- 5% of said values, and having a pH of 6.0 or within +/- 5% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL

polysorbate 80 (Tween 80) or having amounts of each constituent within +/- 5% of said values, and having a pH of 6.0 or within +/- 5% of said value.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) and water or having amounts of each constituent within +/- 5% of said values, and having a pH of 6.0 or within +/- 5% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl) and 0.02% polysorbate 80 (Tween 80) (w/v) or having amounts of each constituent within +/- 1% of said values, and having a pH of 6.0 or within +/- 1% of said value.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl), 0.02% polysorbate 80 (Tween 80) (w/v) and water or having amounts of each constituent within +/- 1% of said values, and having a pH of 6.0 or within +/- 1% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) or having amounts of each constituent within +/- 1% of said values, and having a pH of 6.0 or within +/- 1% of said value.

In an embodiment the liquid pharmaceutical composition is essentially consisting of 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 1.40 mg/mL L-Histidine, 3.34 mg/mL L-Histidine monohydrochloride, 34.16 mg/mL Sucrose, 5.83 mg/mL sodium chloride (NaCl), 0.20 mg/mL polysorbate 80 (Tween 80) and water or having amounts of each constituent within +/- 1% of said values, and having a pH of 6.0 or within +/- 1% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl) or having amounts of each constituent within +/- 20% of said values

and 0.02% polysorbate 80 (Tween 80) (w/v) or having a concentration within +/- 30% of said concentration, and having a pH of 6.0 or within +/- 20% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl) or having amounts of each constituent within +/- 15% of said values and 0.02% polysorbate 80 (Tween 80) (w/v) or having a concentration within +/- 25% of said concentration, and having a pH of 6.0 or within +/- 15% of said value.

In an embodiment the liquid pharmaceutical composition comprises 53 mg/mL of the monoclonal anti-alpha synuclein antibody, 25 mM histidine buffer, 100 mM Sucrose, 100 mM sodium chloride (NaCl) or having amounts of each constituent within +/- 10% of said values and 0.02% polysorbate 80 (Tween 80) (w/v) or having a concentration within +/- 20% of said concentration, and having a pH of 6.0 or within +/- 10% of said value.

In an embodiment the liquid pharmaceutical composition is a stable liquid pharmaceutical composition.

In an embodiment the liquid pharmaceutical composition is a low viscosity liquid pharmaceutical composition.

It will be recognized that one or more features of any embodiments disclosed herein may be combined and/or rearranged within the scope of the invention to produce further embodiments that are also within the scope of the invention. All embodiments are meant to apply to all aspects of the present invention.

SPECIFIC NUMBERED EMBODIMENTS:

1. A method of treating multiple system atrophy (MSA), wherein said method comprises administering a monoclonal anti-alpha synuclein antibody intravenously to a human subject having MSA, at a dose of between 4000 mg to 7000 mg or between 2000 mg to 4300 mg, and wherein said monoclonal anti-alpha synuclein antibody binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

2. The method of treating MSA according to embodiment 1, wherein the human subject has early MSA.

3. The method of treating MSA according to embodiment 1, wherein the human subject has MSA at an early stage.

4. The method of treating MSA according to any of embodiments 1-3, wherein the human subject has an UMSARS total score below 40.

5. The method of treating MSA according to any of embodiments 1-4, wherein the human subject has an UMSARS total score below 40 at treatment initiation.

6. The method of treating MSA according to any of embodiments 1-4, wherein the human subject has an UMSARS total score below 40 at first antibody administration.

7. The method of treating MSA according to embodiment 1, wherein the human subject has MSA-C.

8. The method of treating MSA according to embodiment 1, wherein the human subject has early MSA-C.

9. The method of treating MSA according to embodiment 1, wherein the human subject has MSA-C at an early stage.

10. The method of treating MSA according to embodiment 1, wherein the human subject has MSA-C and an UMSARS total score below 40.

11. The method of treating MSA according to embodiment 1, wherein the human subject has MSA-C and an UMSARS total score below 40 at treatment initiation.

12. The method of treating MSA according to embodiment 1, wherein the human subject has MSA-C and an UMSARS total score below 40 at first antibody administration.

13. The method of treating MSA according to any one of embodiments 1-12, wherein said monoclonal antibody 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**;

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**.

14. The method of treating MSA according to any one of embodiments 1-13, wherein said monoclonal antibody comprises a heavy chain variable domain of **SEQ ID NO:31** and a light chain variable domain of **SEQ ID NO:8**.

15. The method of treating MSA according to any one of embodiments 1-13, wherein said monoclonal antibody comprises a heavy chain variable domain having a sequence of **SEQ ID NO:31** and a light chain variable domain having a sequence of **SEQ ID NO:8**.

16. The method of treating MSA according to any one of embodiments 1-15, wherein said monoclonal antibody is a human antibody.

17. The method of treating MSA according to any one of embodiments 1-16, wherein said monoclonal antibody is a human IgG1 antibody.

18. The method of treating MSA according to any one of embodiments 1-17, wherein said monoclonal antibody is GM37 variant 2 (Amlenetug).

19. The method of treating MSA according to any one of embodiments 1-18, wherein said monoclonal antibody comprises a constant heavy chain domain of **SEQ ID NO:18** and a kappa light chain constant domain of **SEQ ID NO:17**.

20. The method of treating MSA according to any one of embodiments 1-19, wherein said monoclonal antibody is administered about every 4 weeks or about once monthly.

21. The method of treating MSA according to any one of embodiments 1-20, wherein said monoclonal antibody is administered at a dose of about 2100 mg or about 4200 mg.

22. The method of treating MSA according to any one of embodiments 1-21, wherein said monoclonal antibody is administered at a dose of about 2100 mg.

23. The method of treating MSA according to any one of embodiments 1-21, wherein said monoclonal antibody is administered at a dose of about 4200 mg.

24. The method of treating MSA according to any one of embodiments 1-23, wherein the treatment consists of delaying disease progression.

25. The method of treating MSA according to any one of embodiments 1-23, wherein the treatment consists of delaying clinical progression.

26. The method of treating MSA according to any one of embodiments 1-23, wherein the treatment consists of slowing disease progression.

27. The method of treating MSA according to any one of embodiments 1-23, wherein the treatment consists of slowing clinical progression.

28. The method of treating MSA according to any one of embodiments 1-27, wherein the treatment consists of delaying or slowing disease or clinical progression by at least 5%, such as at least 10%, such as at least 15%, such as at least 20%, such as at least 25%, such as at least 30%, such as at least 35%, such as at least 40%, such as at least 45%, such as at least 50%, such as at least 55%, such as at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%, such as at least 85% or such as at least 90%.

29. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is quantified by longitudinal changes from baseline in any of the relevant Unified Multiple System Atrophy Rating Scale (UMSARS) scores or any relevant parts of these scales, such as Part I, Part II, Part III or Part IV, or any single item of any of these scales or a change from baseline in any combination of these UMSARS scales or any combination of single items of these UMSARS scales.

30. The method of treating MSA according to any one of embodiments 1-29, wherein the treatment effect is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I and/or Part II or in the modified UMSARS Part I (mUMSARS) or in the abbreviated UMSARS (aUMSARS) scores.

31. The method of treating MSA according to any one of embodiments 1-30, wherein the treatment effect is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale total score (UMSARS TS).

32. The method of treating MSA according to any one of embodiments 1-30, wherein the treatment effect is quantified by longitudinal changes from baseline in the modified UMSARS (mUMSARS).

33. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI).

34. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the pons.

35. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum white matter.

36. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum gray matter.

37. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least a 19% slowing of clinical progression in MSA measured with the UMSARS Total score.

38. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least a 22% slowing of clinical progression in MSA measured with the UMSARS Part I score.

39. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least a 17% slowing of clinical progression in MSA measured with the UMSARS Part II score.

40. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least a 27% slowing of clinical progression in MSA measured with the modified UMSARS score.

41. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least 50% slowing of clinical progression in MSA-C measured with the modified UMSARS score.

42. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least 50% slowing of clinical progression in MSA-C measured with the UMSARS total score.

43. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least 57% slowing of clinical progression in MSA-C measured with the UMSARS Part I score.

44. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is about at least 41% slowing of clinical progression in MSA-C measured with the UMSARS Part II score.

45. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is at least about a 42% slowing of clinical progression in early MSA measured with the modified UMSARS score.

46. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is at least about a 37% slowing of clinical progression in early MSA measured with the UMSARS total score.

47. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is at least about a 42% slowing of clinical progression in early MSA measured with the UMSARS Part I score.

48. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is at least about a 30% slowing of clinical progression in early MSA measured with the UMSARS Part II score.

49. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a slowing of regional volumetric reduction in the pons by at least about a 1.9% less volume reduction.

50. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.3% less volume reduction.

51. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 1.5% less volume reduction.

52. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in the pons by at least about a 2.4% less volume reduction.

53. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 4.2% less volume reduction.

54. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

55. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in the pons by at least about a 1.2% less volume reduction.

56. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.8% less volume reduction.

57. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

58. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.2 score reduced impairment.

59. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.8 score reduced impairment.

60. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.2 score reduced impairment.

61. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.5 score reduced impairment.

62. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a lowering of neurofilament light chain load in CSF by at least about 16.3%.

63. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a lowering of neurofilament light chain load in CSF by at least about 14.4%.

64. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.4 score reduced impairment.

65. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.8 score reduced impairment.

66. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.3 score reduced impairment.

67. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part I single item "Cutting food/handling utensils" by at least about a 0.7 score reduced impairment.

68. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect is a slowing of impairment as measured with UMSARS Part II single item "arising from chair" by at least about a 0.3 score reduced impairment.

69. The method of treating MSA according to any one of embodiments 1-28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part II single item "arising from chair" by at least about a 1.2 score reduced impairment.

70. The method of treating MSA according to any one of embodiments 1-69, wherein the monoclonal antibody is Amlenetug.

A1. A monoclonal anti-alpha synuclein antibody for use in treating multiple system atrophy (MSA), wherein said use comprises administering a monoclonal anti-alpha synuclein antibody intravenously to a human subject having MSA, at a dose of between 4000 mg to 7000 mg or between 2000 mg to 4300 mg, and wherein said monoclonal anti-alpha synuclein antibody binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

A2. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has early MSA.

A3. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has MSA at an early stage.

A4. The monoclonal anti-alpha synuclein antibody for use according to any of embodiments A1-A3, wherein the human subject has an UMSARS total score below 40.

A5. The monoclonal anti-alpha synuclein antibody for use according to any of embodiments A1-A4, wherein the human subject has an UMSARS total score below 40 at treatment initiation.

A6. The monoclonal anti-alpha synuclein antibody for use according to any of embodiments A1-A4, wherein the human subject has an UMSARS total score below 40 at first antibody administration.

A7. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has MSA-C.

A8. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has early MSA-C.

A9. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has MSA-C at an early stage.

A10. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has MSA-C and an UMSARS total score below 40.

A11. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has MSA-C and an UMSARS total score below 40 at treatment initiation.

A12. The monoclonal anti-alpha synuclein antibody for use according to embodiment A1, wherein the human subject has MSA-C and an UMSARS total score below 40 at first antibody administration.

A13. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A12, wherein said monoclonal antibody 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**;

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**.

A14. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A13, wherein said monoclonal antibody comprises a heavy chain variable domain of **SEQ ID NO:31** and a light chain variable domain of **SEQ ID NO:8**.

A15. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A13, wherein said monoclonal antibody comprises a heavy chain variable domain having a sequence of **SEQ ID NO:31** and a light chain variable domain having a sequence of **SEQ ID NO:8**.

A16. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A15, wherein said monoclonal antibody is a human antibody.

A17. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A16, wherein said monoclonal antibody is a human IgG1 antibody.

A18. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A17, wherein said monoclonal antibody is GM37 variant 2 (Amlenetug).

A19. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A18, wherein said monoclonal antibody comprises a constant heavy chain domain of **SEQ ID NO:18** and a kappa light chain constant domain of **SEQ ID NO:17**.

A20. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A19, wherein said monoclonal antibody is administered about every 4 weeks or about once monthly.

A21. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A20, wherein said monoclonal antibody is administered at a dose of about 2100 mg or about 4200 mg.

A22. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A21, wherein said monoclonal antibody is administered at a dose of about 2100 mg.

A23. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A21, wherein said monoclonal antibody is administered at a dose of about 4200 mg.

A24. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A23, wherein the treatment consists of delaying disease progression.

A25. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A23, wherein the treatment consists of delaying clinical progression.

A26. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A23, wherein the treatment consists of slowing disease progression.

A27. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A23, wherein the treatment consists of slowing clinical progression.

A28. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A27, wherein the treatment consists of delaying or slowing disease or clinical progression by at least 5%, such as at least 10%, such as at least 15%, such as at

least 20%, such as at least 25%, such as at least 30%, such as at least 35%, such as at least 40%, such as at least 45%, such as at least 50%, such as at least 55%, such as at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%, such as at least 85% or such as at least 90%.

A29. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is quantified by longitudinal changes from baseline in any of the relevant Unified Multiple System Atrophy Rating Scale (UMSARS) scores or any relevant parts of these scales, such as Part I, Part II, Part III or Part IV, or any single item of any of these scales or a change from baseline in any combination of these UMSARS scales or any combination of single items of these UMSARS scales.

A30. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A29, wherein the treatment effect is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I and/or Part II or in the modified UMSARS Part I (mUMSARS) or in the abbreviated UMSARS (aUMSARS) scores.

A31. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A30, wherein the treatment effect is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale total score (UMSARS TS).

A32. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A30, wherein the treatment effect is quantified by longitudinal changes from baseline in the modified UMSARS (mUMSARS).

A33. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI).

A34. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the pons.

A35. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum white matter.

A36. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum gray matter.

A37. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least a 19% slowing of clinical progression in MSA measured with the UMSARS Total score.

A38. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least a 22% slowing of clinical progression in MSA measured with the UMSARS Part I score.

A39. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least a 17% slowing of clinical progression in MSA measured with the UMSARS Part II score.

A40. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least a 27% slowing of clinical progression in MSA measured with the modified UMSARS score.

A41. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least 50% slowing of clinical progression in MSA-C measured with the modified UMSARS score.

A42. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least 50% slowing of clinical progression in MSA-C measured with the UMSARS total score.

A43. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least 57% slowing of clinical progression in MSA-C measured with the UMSARS Part I score.

A44. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is about at least 41% slowing of clinical progression in MSA-C measured with the UMSARS Part II score.

A45. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is at least about a 42% slowing of clinical progression in early MSA measured with the modified UMSARS score.

A46. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is at least about a 37% slowing of clinical progression in early MSA measured with the UMSARS total score.

A47. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is at least about a 42% slowing of clinical progression in early MSA measured with the UMSARS Part I score.

A48. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is at least about a 30% slowing of clinical progression in early MSA measured with the UMSARS Part II score.

A49. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a slowing of regional volumetric reduction in the pons by at least about a 1.9% less volume reduction.

A50. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.3% less volume reduction.

A51. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 1.5% less volume reduction.

A52. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in the pons by at least about a 2.4% less volume reduction.

A53. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 4.2% less volume reduction.

A54. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

A55. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in the pons by at least about a 1.2% less volume reduction.

A56. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.8% less volume reduction.

A57. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

A58. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.2 score reduced impairment.

A59. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.8 score reduced impairment.

A60. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.2 score reduced impairment.

A61. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.5 score reduced impairment.

A62. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a lowering of neurofilament light chain load in CSF by at least about 16.3%.

A63. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a lowering of neurofilament light chain load in CSF by at least about 14.4%.

A64. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.4 score reduced impairment.

A65. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.8 score reduced impairment.

A66. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.3 score reduced impairment.

A67. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.7 score reduced impairment.

A68. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by at least about a 0.3 score reduced impairment.

A69. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by at least about a 1.2 score reduced impairment.

A70. The monoclonal anti-alpha synuclein antibody for use according to any one of embodiments A1-A69, wherein the antibody is Amlenetug.

B1. Use of a monoclonal anti-alpha synuclein antibody in the manufacture of a medicament for treating multiple system atrophy (MSA), wherein said treatment comprises administering a monoclonal anti-alpha synuclein antibody intravenously to a human subject having MSA, at a dose of between 4000 mg to 7000 mg or between 2000 mg to 4300 mg, and wherein said monoclonal anti-alpha synuclein antibody binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10).

B2. The use according to embodiment B1, wherein the human subject has early MSA.

B3. The use according to embodiment B1, wherein the human subject has MSA at an early stage.

B4. The use according to any of embodiments B1-B3, wherein the human subject has an UMSARS total score below 40.

B5. The use according to any of embodiments B1-B4, wherein the human subject has an UMSARS total score below 40 at treatment initiation.

B6. The use according to any of embodiments B1-B4, wherein the human subject has an UMSARS total score below 40 at first antibody administration.

B7. The use according to embodiment B1, wherein the human subject has MSA-C.

B8. The use according to embodiment B1, wherein the human subject has early MSA-C.

B9. The use according to embodiment B1, wherein the human subject has MSA-C at an early stage.

B10. The use according to embodiment B1, wherein the human subject has MSA-C and an UMSARS total score below 40.

B11. The use according to embodiment B1, wherein the human subject has MSA-C and an UMSARS total score below 40 at treatment initiation.

B12. The use according to embodiment B1, wherein the human subject has MSA-C and an UMSARS total score below 40 at first antibody administration.

B13. The use according to any one of embodiments B1-B12, wherein said monoclonal antibody 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**;
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**.

B14. The use according to any one of embodiments B1-B13, wherein said monoclonal antibody comprises a heavy chain variable domain of **SEQ ID NO:31** and a light chain variable domain of **SEQ ID NO:8**.

B15. The use according to any one of embodiments B1-B13, wherein said monoclonal antibody comprises a heavy chain variable domain having a sequence of **SEQ ID NO:31** and a light chain variable domain having a sequence of **SEQ ID NO:8**.

B16. The use according to any one of embodiments B1-B15, wherein said monoclonal antibody is a human antibody.

B17. The use according to any one of embodiments B1-B16, wherein said monoclonal antibody is a human IgG1 antibody.

B18. The use according to any one of embodiments B1-B17, wherein said monoclonal antibody is GM37 variant 2 (Amlenetug).

B19. The use according to any one of embodiments B1-B18, wherein said monoclonal antibody comprises a constant heavy chain domain of **SEQ ID NO:18** and a kappa light chain constant domain of **SEQ ID NO:17**.

B20. The use according to any one of embodiments B1-B19, wherein said monoclonal antibody is administered about every 4 weeks or about once monthly.

B21. The use according to any one of embodiments B1-B20, wherein said monoclonal antibody is administered at a dose of about 2100 mg or about 4200 mg.

B22. The use according to any one of embodiments B1-B21, wherein said monoclonal antibody is administered at a dose of about 2100 mg.

B23. The use according to any one of embodiments B1-B21, wherein said monoclonal antibody is administered at a dose of about 4200 mg.

B24. The use according to any one of embodiments B1-B23, wherein the treatment consists of delaying disease progression.

B25. The use according to any one of embodiments B1-B23, wherein the treatment consists of delaying clinical progression.

B26. The use according to any one of embodiments B1-B23, wherein the treatment consists of slowing disease progression.

B27. The use according to any one of embodiments B1-B23, wherein the treatment consists of slowing clinical progression.

B28. The use according to any one of embodiments B1-B27, wherein the treatment consists of delaying or slowing disease or clinical progression by at least 5%, such as at least 10%, such as at least 15%, such as at least 20%, such as at least 25%, such as at least 30%, such as at least 35%, such as at least 40%, such as at least 45%, such as at least 50%, such as at least 55%, such as at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%, such as at least 85% or such as at least 90%.

B29. The use according to any one of embodiments AB-B28, wherein the treatment effect is quantified by longitudinal changes from baseline in any of the relevant Unified Multiple System Atrophy Rating Scale (UMSARS) scores or any relevant parts of these scales, such as Part I, Part II, Part III or Part IV, or any single item of any of these scales or a change from baseline in any combination of these UMSARS scales or any combination of single items of these UMSARS scales.

B30. The use according to any one of embodiments B1-B29, wherein the treatment effect is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale (UMSARS) Part I and/or Part II or in the modified UMSARS Part I (mUMSARS) or in the abbreviated UMSARS (aUMSARS) scores.

B31. The use according to any one of embodiments B1-B30, wherein the treatment effect is quantified by longitudinal changes from baseline in the Unified Multiple System Atrophy Rating Scale total score (UMSARS TS).

B32. The use according to any one of embodiments B1-B30, wherein the treatment effect is quantified by longitudinal changes from baseline in the modified UMSARS (mUMSARS).

B33. The use according to any one of embodiments B1-B28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI).

B34. The use according to any one of embodiments B1-B28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the pons.

B35. The use according to any one of embodiments B1-B28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum white matter.

B36. The use according to any one of embodiments B1-B28, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI) of the cerebellum gray matter.

B37. The according to any one of embodiments B1-B28, wherein the treatment effect is about at least a 19% slowing of clinical progression in MSA measured with the UMSARS Total score.

B38. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least a 22% slowing of clinical progression in MSA measured with the UMSARS Part I score.

B39. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least a 17% slowing of clinical progression in MSA measured with the UMSARS Part II score.

B40. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least a 27% slowing of clinical progression in MSA measured with the modified UMSARS score.

B41. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least 50% slowing of clinical progression in MSA-C measured with the modified UMSARS score.

B42. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least 50% slowing of clinical progression in MSA-C measured with the UMSARS total score.

B43. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least 57% slowing of clinical progression in MSA-C measured with the UMSARS Part I score.

B44. The use according to any one of embodiments B1-B28, wherein the treatment effect is about at least 41% slowing of clinical progression in MSA-C measured with the UMSARS Part II score.

B45. The use according to any one of embodiments B1-B28, wherein the treatment effect is at least about a 42% slowing of clinical progression in early MSA measured with the modified UMSARS score.

B46. The use according to any one of embodiments B1-B28, wherein the treatment effect is at least about a 37% slowing of clinical progression in early MSA measured with the UMSARS total score.

B47. The use according to any one of embodiments B1-B28, wherein the treatment effect is at least about a 42% slowing of clinical progression in early MSA measured with the UMSARS Part I score.

B48. The use according to any one of embodiments B1-B28, wherein the treatment effect is at least about a 30% slowing of clinical progression in early MSA measured with the UMSARS Part II score.

B49. The use according to any one of embodiments B1-B28, wherein the treatment effect is a slowing of regional volumetric reduction in the pons by at least about a 1.9% less volume reduction.

B50. The use according to any one of embodiments B1-B28, wherein the treatment effect is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.3% less volume reduction.

B51. The use according to any one of embodiments B1-B28, wherein the treatment effect is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 1.5% less volume reduction.

B52. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in the pons by at least about a 2.4% less volume reduction.

B53. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 4.2% less volume reduction.

B54. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

B55. The use according to any one of embodiments B1-B28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in the pons by at least about a 1.2% less volume reduction.

B56. The use according to any one of embodiments B1-B28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in cerebellar white matter by at least about a 3.8% less volume reduction.

B57. The use according to any one of embodiments B1-B28, wherein the treatment effect in MSA-C is a slowing of regional volumetric reduction in cerebellar gray matter by at least about a 0.4% less volume reduction.

B58. The use according to any one of embodiments B1-B28, wherein the treatment effect is slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.2 score reduced impairment.

B59. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of impairment as measured with the UMSARS Part IV - Global disability score by at least about a 0.8 score reduced impairment.

B60. The use according to any one of embodiments B1-B28, wherein the treatment effect is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.2 score reduced impairment.

B61. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of impairment as measured with Clinical Global Impression – Severity of Illness score by at least about a 0.5 score reduced impairment.

B62. The use according to any one of embodiments B1-B28, wherein the treatment effect is a lowering of neurofilament light chain load in CSF by at least about 16.3%.

B63. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a lowering of neurofilament light chain load in CSF by at least about 14.4%.

B64. The use according to any one of embodiments B1-B28, wherein the treatment effect is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.4 score reduced impairment.

B65. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part I single item “speech” by at least about a 0.8 score reduced impairment.

B66. The use according to any one of embodiments B1-B28, wherein the treatment effect MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.3 score reduced impairment.

B67. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part I single item “Cutting food/handling utensils” by at least about a 0.7 score reduced impairment.

B68. The use according to any one of embodiments B1-B28, wherein the treatment effect is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by at least about a 0.3 score reduced impairment.

B69. The use according to any one of embodiments B1-B28, wherein the treatment effect in early MSA is a slowing of impairment as measured with UMSARS Part II single item “arising from chair” by at least about a 1.2 score reduced impairment.

B70. The use according to any one of embodiments B1-B69, wherein the monoclonal antibody is Amlenetug.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. Such equivalents are intended to be within the scope of the present invention.

EXPERIMENTAL SECTION – DOSING REGIMENS AND CLINICAL USE IN MSA

The examples provided below serve to facilitate a more complete understanding of the invention. However, the scope of the invention is not limited to specific embodiments disclosed in these Examples, which are for purposes of illustration only, since alternative methods can be utilized to obtain similar results.

Example 1 – Model to establish dosage regimens for antibodies for use according to the invention illustrated by GM37 variant 2

The dosing regimens for antibodies for use according to the invention was obtained by establishing the specific relationship for GM37v2 between the binding to monomeric alpha synuclein and binding to the oligomeric form of alpha synuclein. This specific relationship is unique for each alpha synuclein antibody and is essential to establish clinically relevant dosing regimens which provides the desired target engagement to the pathological forms of alpha synuclein in the CSF of the patient. In vitro, the KD value of binding to the monomer form of alpha synuclein for GM37v2 was measured to 36 nM (5,400 ng/mL) (see example 6A) and the avidity-mediated enhanced KD to the oligomeric forms for GM37v2 was estimated to be approximately 65-fold (64.1+/-5.2) lower (that is, 0.5 nM; 83 ng/mL) (see example 2).
In addition to this fold change between the monomeric and oligomeric binding, detailed PK knowledge of GM37v2 is also required to obtain the dosing regimens. The PK properties was obtained via the experiment disclosed in example 3. GM37 variant 2 was found to have a clearance of approximately 0.25 L/day, such as 0.24 L/day and a T½ of approximately 30 days, such as 29 days.
Target engagement of GM37 variant 2 to alpha-synuclein can be calculated from the percentage free alpha-synuclein in plasma or CSF (not bound to GM37 variant 2).
Figure 6 shows median free alpha synuclein plasma concentrations versus time for healthy subjects and patients. A clear dose related inhibition was observed. The same was observed

for the %free/total alpha synuclein (Figure 7). A good correlation between plasma concentrations of % free/total alpha synuclein and GM37 variant 2 is also seen in Figure 8, where an Emax model (see below) was fitted to the data.

Notably the observed IC50 value was similar to the KD value measured in vitro providing experimental validation of the maximum inhibition Emax model described below.

According to the simple maximum inhibition E_{max} model % free/total relevant for **monomeric** alpha synuclein target engagement is given by:

$$\textbf{\% free/total alpha synuclein}_{mono} = E_{max} \cdot (Css/(KD + Css))$$

Wherein Emax is set to 100%, Css is the estimated mean steady state concentration of GM37v2 and KD is the in vitro measured binding to monomeric alpha synuclein (36 nM for GM37v2).

In order to establish relevant clinical doses of GM37v2 for treating synucleinopathies where the aggregated alpha synuclein is the primary target for the treatment and not the monomeric forms, it is required to adapt this model to take into account the avidity gain of 65-fold between the monomer and the oligomeric binding for GM37v2 – this avidity gain obtained when targeting the aggregates vs. the monomers as described in example 2 and depicted in figure 1. For GM37v2 the avidity gain is 65-fold and hence the model for the aggregated species of alpha synuclein as primary target should employ a KD proxy value which is 65-fold lower than the monomeric KD of 36 nM (36nM/65 = 0.5 nM). In the model below this estimated KD enhancement is denoted "(KD-avidity-gain)".

Accordingly, the E_{max} model % free/total relevant for target engagement of **aggregated** forms of alpha synuclein is given by:

$$\textbf{\% free/total alpha synuclein}_{agg} = E_{max} \cdot (Css/(KD\text{-}avidity\text{-}gain + Css))$$

Css values can be calculated based on the results obtained in example 3:

For example, these parameters: dose = 4200 mg; dosing interval = 28 days; clearance = 0.25 L/day; gives an estimated average plasma Css of (4200mg/28day)/0.25L/day = 600 mg/L = 600 µg/mL.

Correspondingly, the average CSF Css is 0.3% of 600 µg/mL = 1.8 µg/mL, equals 12 nM (because 1 µg/mL = 6.67 nM, see below).

When Emax is set to 100% and the KD-avidity-gain is 0.5 nM it follows that in this specific example where GM37v2 CSF Css = 12 nM, the estimated CSF target engagement to oligomeric/aggregated alpha synuclein is 96% following the below calculation:

% free/total alpha synuclein$_{agg}$ = E_{max}· (Css/(KD-avidity-gain + Css)) =

100%·(12nM/(0.5nM+12nM)) = 96%.

Based on the data summarized above and the value for the fold difference in the affinity/avidity to the target; alpha synuclein monomer versus oligomeric forms found in example 2, the doses of GM37 variant 2 that yield a predicted 85% to 95% target engagement in the CSF at steady state to alpha synuclein oligomeric forms at the following fixed doses (body weight 70 kg): 1050 mg (15 mg/kg), 2100 mg (30 mg/kg), and 4200 mg (60 mg/kg) every 4 weeks were modelled and are presented in **Figure 1;** The plots are based on the predicted average CSF Css of GM37 variant 2 (calculated as dose/dosing interval/clearance as exemplified above) and a fraction in the CSF of 0.3% of the CSF Css. The binding is assumed to follow a simple sigmoid model of the Emax type and 1 nM GM37v2 = 0.15 µg/mL (1 µg/mL = 6.67 nM).

Predictions based on these calculations:

1050 mg IV infusion once every 4 weeks is predicted to maintain GM37 variant 2 concentration in CSF and brain interstitial fluid (ISF) at around IC85, that is the average concentration for 85% of the oligomeric alpha synuclein to be bound.

2100 mg IV infusion once every 4 weeks is predicted to maintain GM37 variant 2 concentration in CSF and brain interstitial fluid (ISF) at around IC90, that is the average concentration for 90% of the oligomeric alpha synuclein to be bound.

4200 mg IV infusion once every 4 weeks is predicted to maintain GM37 variant 2 concentration in CSF and brain interstitial fluid (ISF) at around IC95, that is the average concentration for 95% of the oligomeric alpha synuclein to be bound.

Example 2 – Competition ELISA - Target engagement monomers vs oligomers illustrated by GM37 Variant 2

The binding profile of GM37 Variant 2 to the monomeric and fibril forms of alpha synuclein was characterized in this assay also referred to as a competition ELISA to determine the fold difference between binding to monomeric and fibrillar alpha synuclein.

The assay principle is based on high density coating of monomeric alpha synuclein for capture of unbound anti-alpha synuclein mAb post preincubation with increasing concentrations of either monomer alpha synuclein or alpha synuclein fibrils. The observed IC50 values for either alpha synuclein monomer or alpha synuclein fibrils is thereby a relative

measurement of the differential binding strength to the two representative biologically active species of alpha synuclein. The assay principle is illustrated in **Figure 2**.

Production of preformed fibrils

The alpha synuclein monomer for preformed fibrils (PFFs) was produced from an eukaryotic source and fibrillated according to the protocol published in Polinski et al. J Parkinsons Dis. 2018; 8(2): 303–322.

Briefly, 400 µL monomeric alpha synuclein at 4 mg/mL in PBS was agitated at 37°C by thermomixer at 1000 rpm in a 2 mL round-bottom tube for a duration of 5 days. The fibrillation of the protein was verified by increased fluorescence in response to Thioflavin T and increased hydrodynamic diameter measured by dynamic light scattering (DLS). The fibrils were sonicated by QSonica R800 (Amplitude 50, 20 s on, 10 s off, 10 min) to obtain a monodisperse size distribution (Z-average) below 100 nm measured by DLS. The PFFs were then aliquoted to 10 µL volumes and stored at -80 C until use.

On day one, 384 well plates are coated with alpha synuclein monomer, 1.4 µg/ml, 50 µl per well. The plates were incubated at 4°C. All solutions and plates were kept on ice and transferred directly to the fridge. The assay is continued the following day.

Serial twofold dilutions of alpha synuclein monomers and fibrils, ranging from 60 µM to 7.15 pM, were prepared in blocking buffer in a low bind polypropylene plate. Alpha synuclein fibril preparations were thawed at RT, whereas the alpha synuclein monomer preparations were thawed on ice. Just before use, monomer and fibrillar stock solutions were mixed gently by pipetting half the total volume three times. Equal volumes of mAb (40 ng/ml) were added to all wells containing the dilution series of alpha synuclein, and the low bind plate incubate for 2 hrs at RT with gentle agitation on a vertical plate shaker (300 rpm) to allow antibody-antigen complexes to form. Two wells with blocking buffer were included as blanks and two wells with mAb + blocking buffer were included as positive controls. 1 hr before the above-described pre-incubation is completed, the alpha synuclein coated assay plates were washed three times with PBS-T using the 384-well automated plate washer, and 100 µl of blocking buffer is added to each well and the plates were incubated for 1 hr at RT.

Prior to use, the assay plates were emptied over a sink and thoroughly tapped on a paper towel to ensure that the wells are completely emptied. The pre-incubated samples were added to the assay plates in duplicates of 50µl per well, and the plates were incubated for 10 min at RT.

The plates were washed three times with PBS-T using the 384-well automated plate washer. 50 µl of the secondary goat anti-human – HRP antibody, diluted 1:15.000 in blocking buffer, was added per well followed by incubation for 1 hr at RT.

The plates were washed three times with PBS-T using the 384-well automated plate washer. The two ELISA substrate components were mixed 1:1 in appropriate volumes and 50µl is added to all wells. Immediately after addition the Luminescence signals were quantified in an Envision microtiter plate reader.

IgG binding curves were fitted and IC50 values calculated using equation: Sigmoidal, 4PL, X is log(concentration) Y=Bottom + (Top-Bottom)/(1+((X^HillSlope)/(IC50^Hillslope))).

Results

The binding of GM37 Variant 2 to monomeric and fibrillar alpha synuclein was characterized in a competition ELISA. The analysis was performed in two independent replicates per day which were repeated at three different days, using one monomer alpha synuclein preparation and three different alpha synuclein fibril batches. The used antibody concentration (final 20 ng/ml or 133 pM) was, before this analysis, shown to be in the dynamic range of the antibody titration curve when using a 1.4 µg/ml monomer solution for coating the wells. This enables differentiation of free antibody levels.

Based on the six independent competition ELISA analyses, GM37 Variant 2 has an average IC50 value to monomeric alpha synuclein of 183.9 ± 20.5 nM and an average IC50 value to fibrillar alpha synuclein of 2.9 ± 4 nM (see Table below). Based on these numbers GM37 Variant 2 has an average preference for binding to fibrillar alpha synuclein of 64.1 ± 5.2 fold, about 65 fold.

Table showing the six specific experiments for GM37 Variant 2 binding properties to monomer and fibril alpha synuclein

mAb tested	IC50 monomer alpha synuclein (nM)	IC50 fibrillar alpha synuclein (nM)	Fold preference for fibril binding
GM37 Variant 2	162,2	2,65	61,3
GM37 Variant 2	169,6	2,30	73,7
GM37 Variant 2	211,8	3,28	64,5
GM37 Variant 2	193,0	2,91	66,4
GM37 Variant 2	161,2	2,84	56,8

GM37 Variant 2	205,7	3,32	61,9
Average	**183,9**	**2,9**	**64,1**
SD	*20,5*	*0,4*	*5,2*

As seen in **Figure 3** the GM37 Variant 2 IC50 values are calculated from accurate curve fits and full titration curves of both monomer and alpha synuclein fibrils. In addition, the assay reproducibility across measurements was good with IC50 CV (%) values of 11,2% (monomer alpha synuclein) and 12,3% (fibrillar alpha synuclein). Likewise, the calculated GM37 Variant 2-fold preference for binding to aSN fibrils presented with a low CV value of 8,1%. Noteworthy, the numbers are based on analyses of three different fibril batches, demonstrating the assay stability.

A similar analysis was performed using a Fab fragment derived from GM37v2, to discriminate between the contribution of avidity by the IgG format or the existence of a fibril induced conformational epitope. The Fab fragment has no preference for binding to fibrillar alpha synuclein. Together, these data indicate that the GM37v2 preference for binding to fibrillar alpha synuclein is solely driven by avidity, with no indication of fibrillar selectivity or a specific conformational fibril epitope.

In summary, the competition ELISA experiment showed that GM37 Variant 2 has around 65-fold preferential binding to fibril compared to monomer alpha synuclein; this number can be referred to as an avidity gain in binding and was used for developing the dosage regimen model described in example 1.

Further, the binding affinity/avidity of GM37var2 to MSA and PD brain homogenates enriched for aggregated, insoluble alpha synuclein by ELISA was also evaluated (data not shown). The EC50 of GM37var2 to brain derived alpha synuclein oligomers and fibrils in these samples was shown to be around 0.09-0.16 nM, supporting the clinical relevance of the sub-nanomolar binding to fibrils seen with recombinant material in the experimental setup described above.

Example 3 – Single Ascending Dose (SAD) study for antibodies for use according to the invention illustrated by GM37 variant 2

This was an interventional, randomized, double-blind, sequential-group, placebo-controlled,

single-ascending-dose study. The study was conducted to determine the safety, tolerability, PK, and pharmacodynamic properties of GM37 variant 2 in healthy non-Japanese and Japanese subjects (Part A) and in patients with PD (Part B).

Part A consisted of 6 sequential cohorts (Cohorts A1 to A6):

- Cohorts A1 to A3: 8 healthy subjects per cohort: 6 randomized to GM37v2 and 2 randomized to placebo.
- Cohorts A4 to A6: 11 to 12 healthy subjects per cohort stratified by ethnicity, aiming for an equal number of non-Japanese and Japanese; per ethnic group: up to 4 subjects randomized to GM37v2 and 1 to 2 subjects randomized to placebo.

Part B consisted of two cohorts (Cohorts B1 and B2):

- Cohorts B1 and B2: 7 to 8 patients with Parkinson's disease (PD): 6 patients randomized to GM37v2 and 1 to 2 patients randomized to placebo.

- The dose range was 75 to 9000 mg; the exact dose increments were decided at dosing conferences. Part A: 6 doses tested; 75mg - 225mg - 750 mg - 2250 mg - 4500mg - 9000mg in healthy subjects. Part B: 2 doses tested; 2250mg and 9000mg in PD patients.
- The GM37v2 and placebo doses were administered by intravenous (IV) infusions over a 60-minute period (±10 minutes).
- Within each cohort, the first 2 subjects/patients received either GM37v2 or placebo (1:1) and hence served as sentinel subjects/patients to assess safety and tolerability before the remaining subjects/patients were dosed.
- In Cohorts A1, A2, A3, B1, and B2, following the sentinel subjects: up to 6 subjects received GM37v2 or placebo (5:1) at least 14 days after the sentinel subjects were dosed and their safety data reviewed. The 6 subjects were dosed at staggered intervals, with a maximum of 3 subjects initiated on the same day (with a maximum of 30 minutes overlap between each infusion) and a minimum of 1 day before initiation of the next staggered group.

- In Cohorts A4, A5, and A6, following the sentinel subjects: between 9 to 10 subjects received GM37v2 or placebo (7:2 in Cohort A4, 7:3 in Cohort A5, and 6:3 in Cohort A6) at least 14 days after the sentinel subjects were dosed and their safety data reviewed. The 10 subjects were dosed at staggered intervals, with a maximum of 3 subjects initiated on the same day (with a maximum of 30 minutes overlap between each infusion) and a minimum of 1 day before initiation of the next staggered group.
- Parts A and B were run in parallel. However, the dose administered to patients with PD in Cohort B1 did not exceed the dose tested in healthy subjects in Part A. Initiation of Cohort B1 was based on the safety and tolerability evaluation of the first 6 subjects in Cohort A4 (that is, at the same dose).
- All subjects/patients were screened within 3 and 7 weeks, respectively, before administration of GM37v2. Eligible subjects/patients were confined to the clinic from 2 days before dosing (Day -2) until 3 days after dosing (afternoon of Day 4). The subjects/patients subsequently returned at regular intervals for outpatient visits until the final assessment 12 weeks after administration of IMP.
- Safety and tolerability were assessed throughout the study.
- Blinded safety and tolerability data, preliminary pharmacokinetic data, and preliminary peripheral blood and CSF pharmacodynamic (target engagement) data for Part A were evaluated and discussed at dosing conferences prior to dose escalation and initiation of each cohort in Part A. Dose escalation for the second cohort in Part A (Cohort A2) was based on the evaluation of 4 weeks of safety data from the first cohort (Cohort A1); for each subsequent cohort in Part A, dose escalation was based on at least 2 weeks of safety data from the previous cohorts in Part A.

Pharmacokinetic results:

Following an IV infusion of GM37v2, median tmax occurred within 8 to 90 minutes after the end of infusion (individual range 1.00 to 5.00 hours post start of infusion) in non-Japanese subjects, slightly later, within 15 to 150 minutes after the end of infusion (individual range 1.00 to 5.00 hours post start of infusion) in Japanese subjects, and within 38 to 45 minutes after the end of infusion (individual range 1.00 to 5.00 hours post start of infusion) in patients with PD. By the end of infusion (1 hour post-dose), Cmax had not been reached in the majority of subjects/patients (that is, 35 of the 41 subjects who received GM37v2 in Part A

and 10 of the 12 patients who received GM37v2 in Part B). There was no apparent effect of GM37v2 dose on tmax for healthy subjects (Japanese or non-Japanese) or patients with PD, with similar median values and overlapping ranges between the dose groups.

- Following Cmax, the "free" concentration of GM37v2 in plasma declined in a multi-phasic manner and was quantifiable up to the last collected pharmacokinetic sample for all subjects/patients (Day 84 for all except 1 subject in Cohort A5 who's last sample collected on Day 63) in both Parts A and B.
- Clearance was found to be an approximated overall mean CL of 0.01 L/h (0.24 L/d) across all dose groups and parts of the study (range 0.00883 to 0.0121 L/h) and with an approximated overall mean t1/2 of approximately 700 hours (29 days; range 565 to 843 hours); for comparison, endogenous immunoglobulin G1 has a CL of 0.21 L/d and a t1/2 of 21 days.
- The exposure (Cmax and AUCs) of GM37v2 was comparable between Japanese and non-Japanese subjects and between healthy subjects and patients with PD. Half-life, clearance, and volume of distribution were comparable at all doses as well as in Japanese and non-Japanese subjects and between healthy subjects and patients with PD.
- The pharmacokinetics of "free" GM37v2 was linear, with an increase in dose over the 75 to 9000 mg dose range in Part A and the 2250 to 9000 mg dose range in Part B resulting in approximately dose-proportional increases in exposure.
- "Free" GM37v2 crossed the blood brain barrier and was detectable in all CSF samples collected on Days 3 and 21 from subjects/patients in Parts A and B, with the exception of 1 subject (75 mg GM37v2) where "free" GM37v2 was below the limit of quantification in CSF on both Days 3 and 21. The CSF:plasma ratios were between 0.0955% to 0.137% on Day 3 and between 0.164% to 0.512% on Day 21. The CSF:plasma ratios were comparable at all doses and between healthy subjects and patients with PD.
- The median (including quartiles) plasma concentration (ng/mL) of GM37 variant 2 for healthy subjects (Cohort A1 to A6) and patients (Cohort B1 to B2) at each dose level versus time is depicted in Figure 4 a and b.

Pharmacodynamic Results

In both Parts A and B, a dose-dependent reduction in "free" alpha synuclein in plasma, as a result of GM37v2 binding, was observed starting immediately after the infusion of GM37v2. A similar pattern was evident for free:total alpha synuclein but with apparently less variability (figure 6 and 7). There was a transient increase in "total" alpha synuclein

concentrations following all doses of GM37v2, presumably due to binding to GM37v2, returning to baseline prior to Day 84.

- There was no apparent difference in "free" or "total" plasma alpha synuclein levels between Japanese and non-Japanese subjects in the 2250, 4500, and 9000 mg dose groups.
- The mean "free" alpha synuclein levels in plasma had not returned to baseline by the last sampling time on Day 84 for healthy subjects in Part A or patients with PD in Part B.
- There was a small dose-dependent reduction in mean free:total alpha synuclein CSF ratios on Day 3, both in healthy subjects in Part A at the highest doses of GM37v2 (4500 and 9000 mg) and in patients with PD in Part B.
- In Part A, the mean change from baseline in free:total alpha synuclein CSF ratios on Day 3 ranged between -27.9% and 8.06% with the largest decreases (-6.56% and -27.9%) occurring at the highest 4500 and 9000 mg doses. On Day 21, the mean free:total ratio of alpha synuclein decreased from baseline in the placebo (-2.15%) and the 225 to 4500 mg GM37v2 dose groups by between -1.7% to -15.1%. In Part B, the ratios changed from baseline by -8.08% on Day 3 for the 2250 mg dose of GM37v2 and -38.8% on Day 3 and -36.6% on Day 21 for the 9000 mg dose GM37v2.
- "Free" plasma alpha synuclein and plasma free:total alpha synuclein could be fitted to maximum inhibition (Emax) models where increasing concentrations of GM37v2 were related to lower plasma "free" synuclein levels and free:total plasma alpha synuclein ratios. The estimated drug concentration required to produce 50% of maximal inhibition values were 11049 ng/mL for "free" plasma alpha synuclein and 6917 ng/mL for free:total plasma alpha synuclein ratios (figure 8).

Target engagement results:

In addition to the target engagement of the monomeric alpha synuclein in plasma (figure 8), the antibodies for use according to the invention were also surprisingly able to show target engagement to monomeric alpha synuclein in CSF of parkinson's patients after a single dose with GM37v2 (Figure 11). To the best of our knowledge this is the first time that such target engagement has been demonstrated in clinical studies with antibodies against alpha synuclein although other such antibodies with similar or stronger monomeric binding have been tested in the clinical. E.g., Prasinezumab (PRX002 or 9E4) has been reported to have 20 nM binding to monomeric alpha synuclein, but no effect was seen on free alpha synuclein in

CSF in a clinical trial of this antibody including Parkinson's patients and doses between 0.3 mg/kg and 60 mg/kg (Jankovic et al., JAMA Neurol. 2018 Oct; 75(10): 1206–1214).

The high dose in the SAD study (9000 mg) described above was chosen to reach concentrations in CSF that are comparable to those expected after multiple dosing with 4500 mg dose after accumulation of the antibody. Figure 11 shows the change from baseline in % of free/total alpha synuclein measured in CSF samples obtained on day 3 and 21 from patients with parkinson's disease, with around 36% reduction in free/total monomeric alpha synuclein form baseline at the 9000 mg dose. As the binding of GM37v2 to oligomeric form is approximately 65-fold higher, this supports the estimation that even much higher target engagement of aggregated, oligomeric alpha synuclein in the CNS may be achieved, up to the 95% as estimated by the model (see Figure 1 and example 1). These data support that the dosing regimens of the present invention will be able to slow disease progression of synucleinopathies by neutralisation and clearance of oligomeric alpha synuclein bound with antibody in the extracellular matrix.

Example 4 - Population PK (PopPK) analysis from data collected in Example 3

The objective of the PopPK analysis was to obtain PK data to support the dose selected for the

Clinical investigation in patients with synucleinopathies. The PopPK model was developed to describe the time course of GM37 variant 2 PK following single dosing in healthy subjects and to explore the impact of covariates on relevant PK parameters.

In total, 694 PK measurements from 41 subjects from Part A (Cohorts A1 to A6) were included in the PopPK analysis. The GM37 variant 2 plasma concentrations were analysed using nonlinear mixed effects methods. First, a structural model was developed, starting from a simple one-compartment model and continuing with increasing complexity. Different interindividual variability (IIV) models and different residual variability models were investigated to arrive at a stable structural model. Subsequently, covariate relationships were examined in a stepwise procedure (forward inclusion step using a significance criterion of $p < 0.01$ followed by a backward elimination step using a significance criterion of $p < 0.005$) to examine the impact of individual subject characteristics (body weight [WT], height [HT], age, sex, race, and baseline alpha synuclein) on model parameters. Model selection was informed using the objective function value, by the evaluation of numerical checks (such as parameter

estimates and respective precision), graphical goodness-of-fit checks, and scientific and physiological plausibility.

Results of PopPK

The dose-normalized GM37 variant 2 plasma concentrations versus time (log-scale) are presented in **Figure 5** (all subjects); solid line is mean, grey line and circles are individual data. No obvious deviation from dose linearity was seen.

The overall PK profile of GM37 variant 2 was described by a three-compartment model with first order elimination from the central compartment. CL (clearance) and Vss (volume of distribution) were estimated to 0.254 L/day and 8.64 L, respectively. The GM37 variant 2 geometric mean terminal elimination t1/2 was estimated to 30.5 days (17.5% CV). IIV was estimated to 16.1% CV for CL and 10.1% CV for V1 (central volume of distribution). The residual unexplained variability was low (6.91%). There was no significant relationship between predicted individual CL and dose, confirming the dose-proportional PK of GM37 variant 2. ADAs were detected in 3 of 41 subjects receiving GM37 variant 2; No apparent difference in GM37 variant 2 PK was seen in these subjects. Among the primary covariates (WT, HT, age, sex, race (including Japanese), albumin, and baseline alpha synuclein), only WT and HT had a statistically significant impact on the PK parameters.

WT had the largest impact on PK parameters with 25% lower CL in a reference subject with the 5th percentile of the baseline covariate value and 24% higher CL in a reference subject with the 95th percentile of the baseline covariate value. The impact of WT on exposure (AUCss and Cmax;ss) at steady state was considered modest (approximately 0.8 to 1.3-fold for AUCss) at the 5th and 95th percentiles of the baseline covariate distribution as compared to the reference subject (74.6 kg and 171 cm), supporting flat fixed dosing.

The final model demonstrated appropriate agreement between predicted and observed data values.

Example 6 – Antibodies for use according to the invention and their binding to human alpha synuclein

Using a competition ELISA experiment we evaluated the impact that change at residue 54 would have on the ability of GM37wt to bind alpha synuclein in solution. By evaluating the concentration of synuclein able to inhibit binding of the antibody to synuclein coated ELISA plates we showed that GM37 variants maintained the same binding properties and bind to

alpha synuclein with and IC50s of 1-2nM in this specific assay design (**Figure 9**). The competition assay was performed using preincubation of a fixed concentration (0.3 µg/ml) of each of the following antibodies, GM37 (named GM 37wt), GM37 variant1, GM37 variant2 and GM37 variant3 with a range of 0-1000 nM human alpha synuclein for 60 minutes at room temperature. The remaining unbound antibody was captured and measured on ELISA plates coated with 100 ng/ml of recombinant human alpha synuclein using an anti-human detection antibody by electro-chemiluminescence (MSD, Gathersburg, MD). The IC50s of the interaction are 1.9 nM, 1.6 nM, 2.1 nM and 1.4 nM for GM37, GM37 variant 1, GM37 variant 2 and GM37 variant 3, respectively in this specific assay (as determined using Prism Graphpad®).

Example 6A – Determination of exact KD for binding of GM37v2 to monomeric alpha synuclein

The exact KD value of the binding of GM37 variant 2 to monomeric α-synuclein was measured using repeated SPR analyses with a standardized set-up.

The SPR set-up were as follows: The equivalence of ~3000 RU anti-human IgG antibody were amine coupled to the alpha synuclein antibody on a CM4 chip following the protocol from GE (Cat# BR1008-39 from GE Healthcare). The alpha synuclein antibody was diluted to 1 µg/ml and injected with contact time of 30 s to obtain capture levels of ~ 50-200 RU, using either PBS-P with additives: 1 mg/ml BSA (A7979-Sigma Aldrich) and additional 0.05% P20 (total 0.1%) or HBS-P with additives: 5 mg/ml BSA, and additional 0.05% P20 (total 0.1%) as running buffer.

Monomeric α-synuclein was used in a 3-fold dilution series from max 600 nM. The removal (regeneration) of captured antibodies was achieved by injection of 3M MgCl2 regeneration buffers provided in the capture Ab kits (GE Healthcare). The assay running was either PBS-P with additives: 1mg/ml BSA (A7979-Sigma Aldrich) and additional 0.05% P20 (total 0.1%) or HBS-P with additives: 5mg/ml BSA, and additional 0.05% P20 (total 0.1%).

The data were analyzed using Biacore S200 Evaluation software 1.1. The KD and kinetic parameters were determination by global fit of sensorgrams to 1:1 kinetics model. The results of the repeated analysis are given in the table below:

Experi-ment #	Antibody	Monomeric alpha synuclein	Ka (1/Ms)	Kd (1/s)	KD (nM)	Chi (RU)	Stoichio-metry

1	GM37 variant 2	Ab51189	7.40E+05	0.03	45	0.27	1.5
2	GM37 variant 2	Ab51189	4.60E+05	0.02	49	0.06	1.4
3	GM37 variant 2	Ab51189	6.70E+05	0.03	44	0.09	1.4
4	GM37 variant 2	Ab51189	5.80E+05	0.02	30	0.46	1.7
5	GM37 variant 2	Ab51189	1.00E+06	0.03	29	0.06	1.6
6	GM37 variant 2	Ab51189	1.43E+06	0.02	31	0.05	1.9
7	GM37 variant 2	Ab51189	7.20E+05	0.05	32	0.06	1.1
8	GM37 variant 2	Ab51189	6.90E+05	0.02	35	0.10	1.9
9	GM37 variant 2	Ab51189	7.00E+05	0.02	28	0.08	1.8
10	GM37 variant 2	Ab51189	6.70E+05	0.02	33	0.16	1.7
11	GM37 variant 2	Ab51189	6.00E+05	0.02	35	0.08	1.5

Based on repeated SPR analyses using a standardized set-up, the binding of GM37 variant 2 to monomeric α-synuclein has an average measured KD of 36nM (S.D 7nM).

Similar KD values were found for binding of GM37 variant 2 to human, rabbit and rodent monomeric alpha synuclein (data not shown), and hence this parameter was stable and reproducible across measurements from different species. These data support that the modelling underlaying performed to reach the dosing regimens of the present invention are based on well-established binding properties of GM37v2 and hence support the validity of the estimations for e.g. CSF/ISF target engagement of aggregated alpha synuclein.

Example 7 - Ability of the antibodies for use according to the invention to block synuclein seeding activity in a culture of primary neurons

The level of seeding was measured using an antibody specific for phospho-synuclein. GM37 (named GM 37wt), GM37 variant1, GM37 variant2 and GM37 variant 3 were all able to block seeding as measured by the phospho-synuclein signal (**Figure 10**). Furthermore, the level of inhibition was the same for all 4 antibodies. This cell based data further confirms the binding data that amino acid 54 in the VH domain is not required for binding affinity to human alpha synuclein or for inhibition of seeding in a primary cell based assay. Furthermore, we found that all three of these antibodies were capable of production using standard expression and purification methods. Interestingly one of the variants N54Q showed improvement in production over the other variants, which is of great importance when the antibody is to be produced commercially on large scale. These data support the possibility of reducing the potential risk of deamidation by replacing asparagine (N) with another amino acid without concern over the loss of potency.

Several studies have shown that exogenous addition of recombinant alpha synuclein fibrillar aggregates can enter cells and recruit endogenous alpha synuclein and induce alpha synuclein aggregation and phosphorylation in vitro and in vivo, which resemble LB. (Volpicelli-Daley et al. 2011, Luk et al. 2012a, Luk et al. 2012b, Recasens et al. 2013, Peelaerts et al. 2015). To study seeding of endogenous mouse alpha synuclein by recombinant alpha synuclein seeds, mouse primary cortical neurons prepared as above are plated in 96 well plates (15,000 cells per well). On day 5 in vitro culture (DIV), 50% of media is changed and supplemented with cytosine arabinoside (final conc. of 1uM). On DIV 6, half of the media is changed with glia conditioned media along with alpha synuclein fibrillary material, either crude fibril seeds or pure seeds. The crude fibril seeds are made from recombinant monomeric human alpha synuclein, which was isolated from bacteria and the monomers were filtered through an Amicon Ultra 100.000 cut off filter (Millipore cat. No UFC510096) and adjusted to concentration of 1mg/ml in PBS, pH 7.4. To make fibril crude seeds, the monomer solution was incubated in thermomixer at 37C with continuous mixing (800rpm) until plateau is reached (evaluated by daily measures with Thioflavin S). To minimize evaporation a drop of mineral oil was added to cover the solution. The total time for incubation was 5-7 days, The pure seeds are made from crude fibril seeds that are centrifuged to purify them and the aggregated pellet is resuspended in fresh PBS and sonicated. The antibodies are added once on DIV 6 along with alpha synuclein crude seeds.

Half of the media in the primary neurons is replaced with glia conditioned media every week to maintain them up to DIV21. The neurons are fixed and stained for Phospho-synuclein using a rabbit antibody specific for phosphorylation of alpha synuclein at amino acid S129 (abcam 51253), followed by a fluorescently labelled anti-rabbit antibody, fluorescence is quantified using automated fluorescent microscopy, Cellomics Arrayscan. Nuclei were detected in one channel and defined the number of valid cells. Phosphorylated alpha synuclein spots were detected in another channel in a pre-defined ring-formed area surrounding the nucleus, thus representing the cytoplasm of the cells. The average number of spots per cell was calculated.

For fractionation studies cells were harvested in phosphate buffered saline solution (PBS) and centrifuged. Pellet was resuspended in 1% triton buffer with protease inhibitors. Samples were kept on ice for 15 min. followed by sonication. The samples were centrifuged at 100,000x g for 30 min. at 4C. The supernatant is collected and labelled as soluble fraction. The pellet was washed once in triton buffer and re-suspended in 1% SDS buffer followed by sonication. Samples were centrifuged again at 100,000xg for 30 min. The supernatant is collected as insoluble fraction. The protein concentrations were measured and samples were run on 4-12% SDS_PAGE gel, blotted on membranes and alpha synuclein and phosphorylated alpha synuclein (S129P) are detected by 4B12/1904 antibody (Thermo scientific: MA1-90346-human synuclein), S129P-asyn antibody (abcam 51253) and mouse synuclein antibody (cell signalling- D37A6), respectively.

To test if antibodies can inhibit seeding, alpha synuclein seeds were used at conc. of 6.6 nM (10ng/ well). Different concentration of antibody and alpha synuclein seeds were added together on DIV 6, to make a dose response (starting from highest antibody conc. at 133 nM down to 133 pM). The neurons were again fixed and stained for Phospho-synuclein (abcam 51253) and fluorescence from cells was quantified using automated fluorescent microscopy, Cellomics arrayscan. The spots/puncta per cell were counted in Cellomics arrayscan. Both antibody GM37, GM37v2 and antibody GM285 reduced alpha synuclein phosphorylation in neurons in a dose dependent manner with similar maximal inhibition for GM37, GM37v2 and 285 (around 70-75%) and IC50 around 5 nM. Fractionation of the cellular proteins to soluble and insoluble fraction after treatment with antibody at the highest concentration (133 nM) shows that both antibodies GM37, GM37v2 and GM285 inhibited the truncation of the recombinant crude seeds and accumulation of C terminally truncated fragment (CT a-syn),

and reduced the accumulation of phosphorylated endogenous mouse alpha synuclein and aggregated forms of mouse alpha synuclein in the insoluble fraction.

Example 7A – Free and total alpha synuclein quantification in human CSF and plasma

Free (unbound) and total alpha synuclein levels were measured in CSF and plasma using an ECLIA (MSD) quantification assay. An MSD Gold streptavidin plate was washed three times with wash buffer (300 µl/well), followed by well emptying. In the free assay, all wells were subsequently blocked with 150 µl Superblock T20 for 1 hr at room temperature, 500 RPM, followed by addition of 50 µl of 1 ng/ml coating antibody (GM37v2) in PBS. In the total assay, the plate was simultaneously blocked and coated with 25 uL of 1 ng/ml coating antibody (GM37v2) in diluent 49. After 1 hr of incubation at room temperature, 500 RPM, the plate was again washed three times with wash buffer (300 uL/well), followed by well emptying. Next 25 ul detection antibody was added to all wells together with 25 uL diluted samples, alpha synuclein calibration curve (4 ng/mL – 0.030 ng/ml) and QC samples in duplicates. In the free alpha synuclein assay the samples were prediluted 5x in diluent 49, whereas in the total alpha synuclein assay, the samples were pre-diluted 500x in diluent 49 followed by 10 min heat treatment at 95°C, 500 RPM and centrifugation of the samples at 13.000 RPM at room temperature for 10 min prior to transfer to the assay plates. Samples, calibrators, QC samples and detection mAb were incubated for 2 hrs at room temperature, 500 RPM. Subsequently, the plate was washed three times with wash buffer (300 µL/well), followed by well emptying and addition of 150 µl Read Buffer T (1x) to all wells of the plate. The ELC response was measured using a QuickPlex SQ 120 within 5 minutes after the read buffer was added to the MSD streptavidin plate. Alpha synuclein sample levels were interpolated using a 4 PL curve fit of the calibration curve.

Example 8 – Clinical efficacy of the antibodies for use according to the invention for treating MSA

The clinical efficacy or treatment effect of the clinical use of the anti-alpha synuclein antibody GM37v2 (Amlenetug) was confirmed in a randomized, double-blind, placebo-controlled clinical trial.

Specifically, the trial employed a dosage regimen of a fixed GM37var2 (Amlenetug) dose of 4200 mg administered intravenously every 4 weeks for a minimum of 48 weeks and up to 72 weeks to patients suffering from MSA. The trial included 61 MSA patients and consisted of a

double-blind period (DBP) and includes an optional open-label treatment extension (OLE) period lasting up to 44 weeks. Participants in the DBP was randomized to GM37var2 or placebo (2:1). In this trial the antibody administered was Amlenetug.

Key Inclusion Criteria:

- The participant was diagnosed with possible or probable MSA of the multiple system atrophy parkinsonian type (MSA-P) or multiple system atrophy cerebellar type (MSA-C) sub-type at the Screening Visit.
- The participant had onset of motor and/or autonomic (orthostatic or urinary) MSA symptoms within 5 years prior to the Screening Visit in the judgement of the investigator.
- The participant had an UMSARS Part I score ≤16 (omitting item 11 on sexual function) at the Screening Visit.
- The participant had a cognitive performance evaluated by the Montreal Cognitive Assessment (MoCA) with a score ≥22 at the Screening Visit.

Open-label Extension Entry Criteria:

- The participant had completed the EoT Visit and did not withdraw in the DBP.
- The participant had consented to participate in the OLE.
- The participant had completed the DBP within the last 5 months and will be enrolled into the OLE no later than end of Q1 2024.
- The participant was, in the Investigator's opinion, likely to comply with the protocol.
- The participant had not received any other Investigational product since the EoTDBP Visit.

Key Exclusion Criteria:

- The participant had been treated with an anti-α-synuclein monoclonal antibody, mesenchymal stem cells or an inhibitor of α-synuclein aggregation within the last 12 months.
- The participant had any past or current treatment with an active vaccine targeting α-synuclein.
- The participant had 2 or more blood relatives with a history of MSA.
- The participant had evidence (clinically or on MRI) and/or history of any clinically significant disease or condition other than MSA (for example, serious neurological disorder, other intracranial disease, or systemic disease).

- The participant had a current diagnosis of movement disorders that could mimic MSA (for example, Parkinson' disease, dementia with Lewy bodies, essential tremor, progressive supranuclear palsy, spinocerebellar ataxia, spastic paraparesis, corticobasal degeneration, or vascular, pharmacological, or post-encephalitic parkinsonism), per investigator discretion.

The outcome measures of the trial were quantified as longitudinal changes from baseline and up to 48 weeks – or up to 72 weeks of treatment. Treatment effects were measured by multiple clinical scales and biomarkers including UMSARS total score (TS); UMSARS Part I; UMSARS Part II; modified UMSARS (mUMSARS); UMSARS Part I and Part II single items such as Speech, Cutting food/handling utensils, and walking; UMSARS Part IV: Global disability; Brain Volume as measured by Volumetric MRI (vMRI) of specific brain areas e.g. pons, cerebellum white matter and cerebellum gray matter; Clinical Global Impression – Severity of Illness (CGI-S) Score; Schwab and England Activities of Daily Living (SE-ADL) Score; Neurofilament Light Chain (NfL) blood concentrations; and Neurofilament Light Chain (NfL) CSF concentrations.

Treatment effects could also be quantified by other methods as described in this disclosure, e.g. change from baseline in Patient Global Impression – Severity of Illness (PGI-S) Score; as change from baseline in Observer-Reported Global Impression – Severity of Illness (OGI-S) Score; as change from baseline in Composite Autonomic Symptom Score Select Change (COMPASS Select Change) Score; as change from baseline in any single item or groups of single items as assessed by the UMSARS Part I and/or Part II Item Scores; as change from baseline in Frequency, Cause, and Consequence of Falls, as assessed by the Fall Diary Periods; as change from baseline in EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Score; as change from baseline in Brain Volume of any brain area(s) as Measured by Volumetric MRI (vMRI); as change from baseline in Tissue Integrity, as Measured by Diffusion-Tensor Imaging (DTI) MRI; as change from baseline in heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III; as change from baseline in gait parameters or frequency of falls, as assessed by digital wearable sensor-based devices that are capable of tracking relevant gait parameters and/or registering falls; as change from baseline in cerebral blood flow, as measured by arterial spin labelling (ASL) MRI; as change from baseline in t-tau CSF concentrations; or as change from baseline in concentration of pathological species of α-synuclein in CSF.

The summarized results from the clinical trial are presented below:

Baseline characteristics:

		Placebo		GM37v2 (Amlenetug)		Total	
N		**21**		**40**		**61**	
Age (years), mean (SD)		59.8	(6.85)	61.4	(8.09)	60.8	(7.67)
Gender (Male), n (%)		11	(52.4)	21	(52.5)	32	(52.5)
Country, n (%)	Japan	5	(23.8)	7	(17.5)	12	(19.7)
	USA	16	(76.2)	33	(82.5)	49	(80.3)
Disease diagnosis, n (%)	MSA-C	13	(61.9)	28	(70.0)	41	(67.2)
	MSA-P	8	(38.1)	12	(30.0)	20	(32.8)
Diagnostic probability, n (%)	Possible	8	(38)	14	(35)	22	(36)
	Probable	13	(62)	26	(65)	39	(64)
Time (years) since onset of symptoms, mean (SD)		3.1	(1.34)	3.5	(1.06)	3.4	(1.17)
UMSARS TS, mean (SD)		37	(7.77)	34.8	(9)	35.5	(8.59)
MRI signs supporting MSA diagnosis, n (%)	No	4	(19.0)	8	(20.0)	12	(19.7)
	Yes	17	(81.0)	32	(80.0)	49	(80.3)
Plasma NfL (pg/mL) at Scr., mean (SD)		26.7	(8.78)	28.2	(13.24)	27.7	(11.84)
CSF sampling at Baseline, n (%)		12	(57)	28	(70)	40	(65.6)
CSF NfL (pg/mL), mean (SD)		3825.9	(1974.79)	4291.7	(1716.19)	4156.8	(1780.31)
SAA+ N=40, n (% of participants with LP)	No	2	(16.7)	6	(21.4)	8	(20)
	Yes (MSA)	10	(83.3)	18	(64.2)	28	(70)
	Yes (PD/DLB)	0	(0)	4	(14.3)	4	(10)

CSF: Cerebrospinal Fluid, DLB: Dementia with Lewy Bodies, MRI: Magnetic Resonance Imaging, MSA: Multiple System Atrophy, NfL: Neurofilament Light chain, LP: lumbar puncture, PD: Parkinson's disease, SAA: α-Synuclein seeding Amplification Assay, UMSARS TS: Unified Multiple System Atrophy Rating Scale Total Score.

Summary table 1: Bayesian Progression Model for change-from-baseline in UMSARS up to Week 72, Full analysis set (FAS) and by sub-groups

UMSARS domain	Effect parameter (2.5; 97.5 pct)[1]	%-slowing (compared to placebo)	Pr(theta2<1)[2]	Pr(theta2<0.8)[3]
FAS (n=61; GM37v2(Amlenetug)/placebo=40/21)				
- UMSARS TS	0.81 [0.56; 1.13]	19%	0.894	0.471
- UMSARS Part I	0.78 [0.53; 1.11]	22%	0.916	0.564
- UMSARS Part II	0.83 [0.57; 1.20]	17%	0.844	0.423
- mUMSARS	0.73 [0.51; 1.01]	27%	0.970	0.709
Sub-group: MSA-C (n=42; GM37v2(Amlenetug)/placebo=29/13)				
- UMSARS TS	0.50 [0.30; 0.81]	50%	0.998	0.973
- UMSARS Part I	0.43 [0.24; 0.76]	57%	0.999	0.984
- UMSARS Part II	0.59 [0.34; 0.95]	41%	0.984	0.897
- mUMSARS	0.50 [0.29; 0.80]	50%	0.998	0.974
Sub-group: MSA-P (n=20; GM37v2(Amlenetug)/placebo=12/8)				
- UMSARS TS	0.95 [0.54; 1.60]	5%	0.570	0.258
- UMSARS Part I	0.85 [0.40; 1.63]	15%	0.672	0.429
- UMSARS Part II	0.82 [0.43; 1.47]	18%	0.748	0.462
- mUMSARS	0.92 [0.42; 1.67]	8%	0.594	0.346
Sub-group: UMSARS TS Baseline (BL) score < 40 (n=42; GM37v2(Amlenetug)/placebo=30/12)				
- UMSARS TS	0.63 [0.41; 0.94]	37%	0.989	0.877
- UMSARS Part I	0.58 [0.35; 0.90]	42%	0.993	0.927
- UMSARS Part II	0.70 [0.44; 1.06]	30%	0.955	0.736
- mUMSARS	0.58 [0.36; 0.87]	42%	0.996	0.935

[1] median of posterior for effect parameter theta2 defined as 1-%slowing presented with 2.5 and 97.5 percentiles. Region and screening plasma NfL level used as covariates.
[2] probability for theta2 < 1; meaning the probability for GM37v2 (Amlenetug) is slowing the clinical progression compared to placebo.
[3] probability for theta2 < 0.8; meaning the probability for GM37v2 (Amlenetug) is slowing the clinical progression compared to placebo with at least 20%.

Full analysis set (FAS) results:

The results presented in summary table 1 shows a 19% slowing of clinical progression in GM37v2 (Amlenetug) treated MSA patients compared to placebo when effect is measured on the UMSARS TS – the Probability of slowing clinical progression as measured by UMSARS TS was 89.4% (see also figure 12).

Further, the effect was a 22% and 17% slowing of clinical progression when measuring effect with UMSARS part I and II, respectively, with a probability of slowing clinical progression of 91.6% and 84.4%, respectively (see also figures 13 and 14).

Using the mUMSARS scale to measure treatment effect showed a 27% slowing of clinical progression in the active compared to placebo (see also figure 15). The probability of slowing clinical progression as measured by mUMSARS was 96.9% and the probability of 20% slowing was 70.9%.

Sub-groups results:

The results presented in summary table 1 shows a 50 % slowing of clinical progression in GM37v2 (Amlenetug) treated MSA-C patients compared to placebo when effect is measured on the mUMSARS (see also figure 16). The probability of slowing clinical progression was 99.8% in this analysis.

Further a 42% slowing of clinical progression was observed in an earlier subgroup of MSA patients, i.e. patients with a baseline UMSARS score of below 40, compared to placebo when effect is measured on the mUMSARS (see also figure 17). The probability of slowing clinical progression was 98.9% in this analysis.

Summary table 2: Mixed models for repeated measures (MMRM) for change-from-baseline in secondary clinical endpoints at Week 48, Full analysis set (FAS) and by sub-groups

Outcome measure / UMSARS domain	**Placebo: Week 48 cfb LSMEAN (SE)[1]**	**GM37v2 (Amlenetug): Week 48 cfb LSMEAN (SE)[1]**	**Week 48 difference (95% CI)**
FAS (n=61; GM37v2(Amlenetug)/placebo=40/21)			
- CGI-S	0.58 (0.17)	0.34 (0.14)	-0.24 (-0.52; 0.04)
- SE-ADL	-23.56 (7.40)	-20.82 (6.52)	2.74 (-7.90; 13.38)
- UMSARS Part IV: Global disability	1.35 (0.35)	1.13 (0.30)	-0.22 (-0.76; 0.32)
Sub-group: MSA-C (n=42; GM37v2(Amlenetug)/placebo=30/12)			
- CGI-S	-	-	-
- SE-ADL	-	-	-
- UMSARS Part IV: Global disability	-	-	-
Sub-group: UMSARS TS Baseline (BL) score < 40 (n=42; GM37v2(Amlenetug)/placebo=30/12)			
- CGI-S	0.84 (0.18)	0.36 (0.13)	-0.48 (-0.81; -0.14)
- SE-ADL	-24.01 (7.10)	-20.76 (5.82)	3.25 (-8.93; 15.44)
- UMSARS Part IV: Global disability	1.87 (0.38)	1.08 (0.29)	-0.79 (-1.48; -0.10)

[1] Mean estimated change-from-baseline (cfb) and standard error (SE) from the MMRM adjusted for baseline UMSARS, region and screening plasma NfL level.
[2] Daily adjusted falls as collected by the fall diary and adjusted for compliance.

The results presented in summary table 2 shows a directional trend in the change from baseline favouring the active group having a better outcome measure than the placebo treated group (see also figure 18).

Summary table 3: Mixed models for repeated measures (MMRM) for change-from-baseline in UMSARS Part I and Part II single items at Week 48, Full analysis set (FAS) and by sub-group

UMSARS domain	Placebo: Week 48 cfb LSMEAN (SE)[1]	GM37v2 (Amlenetug): Week 48 cfb LSMEAN (SE)[1]	Week 48 difference (95% CI)
FAS (n=61; GM37v2(Amlenetug)/placebo=40/21)			
Part I – 1. Speech	0.61 (0.26)	0.19 (0.21)	-0.42 (-0.86; 0.02)
2. Swallowing	0.57 (0.30)	0.91 (0.25)	0.34 (-0.18; 0.85)
3. Handwriting	0.74 (0.33)	0.87 (0.28)	0.13 (-0.40; 0.67)
4. Cutting food/handling utensils	0.70 (0.31)	0.38 (0.26)	-0.32 (-0.84; 0.20)
5. Dressing	0.63 (0.30)	0.94 (0.24)	0.31 (-0.24; 0.85)
6. Hygiene	0.73 (0.27)	0.53 (0.22)	-0.20 (-0.72; 0.32)
7. Walking	1.02 (0.27)	0.86 (0.23)	-0.17 (-0.60; 0.26)
8. Falling (past month)	0.36 (0.42)	0.22 (0.36)	-0.14 (-0.83; 0.55)
9. Orthostatic symptoms	0.42 (0.37)	0.38 (0.32)	-0.05 (-0.64; 0.55)
10. Urinary function	0.07 (0.40)	0.32 (0.34)	0.25 (-0.44; 0.94)
11. Sexual function	0.33 (0.44)	0.33 (0.39)	0.00 (-0.66; 0.67)
12. Bowel function	0.47 (0.33)	0.56 (0.28)	0.10 (-0.45; 0.64)
Part II – 1. Facial expression	0.68 (0.30)	0.37 (0.26)	-0.31 (-0.79; 0.17)
2. Speech	0.43 (0.21)	0.31 (0.18)	-0.12 (-0.48; 0.24)
3. Ocular motor dysfunction	0.46 (0.34)	0.36 (0.28)	-0.10 (-0.68; 0.49)
4. Tremor at rest	-0.06 (0.20)	-0.01 (0.16)	0.05 (-0.27; 0.38)
5. Action tremor	-0.23 (0.26)	0.32 (0.22)	0.54 (0.13; 0.95)
6. Increased tone	0.24 (0.36)	0.41 (0.32)	0.16 (-0.40; 0.72)
7. Rapid alternating movements of hands	0.70 (0.27)	0.55 (0.23)	-0.15 (-0.58; 0.28)
8. Finger taps	0.68 (0.24)	0.55 (0.21)	-0.13 (-0.54; 0.27)
9. Leg agility	0.70 (0.26)	0.63 (0.22)	-0.06 (-0.50; 0.37)
10. Heel-knee-shin test	0.21 (0.29)	0.66 (0.24)	0.45 (-0.04; 0.94)
11. Arising from chair	0.92 (0.46)	0.58 (0.39)	-0.34 (-1.08; 0.40)
12. Posture	0.63 (0.29)	0.21 (0.24)	-0.42 (-0.92; 0.08)
13. Body sway	0.86 (0.43)	0.61 (0.36)	-0.24 (-0.94; 0.46)
14. Gait	1.00 (0.23)	0.81 (0.21)	-0.19 (-0.54; 0.16)
Sub-group: UMSARS TS Baseline (BL) score < 40 (n=42; GM37v2(Amlenetug)/placebo=30/12)			
Part I – 1. Speech	0.96 (0.33)	0.22 (0.24)	-0.75 (-1.39; -0.10)
2. Swallowing	0.67 (0.35)	0.84 (0.25)	0.16 (-0.53; 0.86)
3. Handwriting	0.60 (0.40)	0.86 (0.30)	0.27 (-0.45; 0.99)
4. Cutting food/handling utensils	1.03 (0.34)	0.35 (0.24)	-0.68 (-1.35; -0.01)
5. Dressing	0.90 (0.36)	1.01 (0.26)	0.12 (-0.63; 0.87)
6. Hygiene	0.98 (0.34)	0.39 (0.23)	-0.59 (-1.30; 0.11)
7. Walking	1.28 (0.32)	0.87 (0.25)	-0.41 (-1.02; 0.21)
8. Falling (past month)	0.22 (0.44)	0.19 (0.32)	-0.03 (-0.86; 0.81)
9. Orthostatic symptoms	0.61 (0.36)	0.36 (0.27)	-0.25 (-0.94; 0.44)
10. Urinary function	0.18 (0.45)	0.16 (0.34)	-0.01 (-0.92; 0.89)
11. Sexual function	0.25 (0.52)	0.13 (0.42)	-0.11 (-1.06; 0.83)
12. Bowel function	0.40 (0.40)	0.55 (0.29)	0.15 (-0.59; 0.89)
Part II – 1. Facial expression	0.70 (0.35)	0.41 (0.27)	-0.29 (-0.94; 0.36)
2. Speech	0.67 (0.22)	0.39 (0.17)	-0.28 (-0.69; 0.14)
3. Ocular motor dysfunction	0.36 (0.39)	0.28 (0.28)	-0.08 (-0.83; 0.67)

UMSARS domain	Placebo: Week 48 cfb LSMEAN (SE)[1]	GM37v2 (Amlenetug): Week 48 cfb LSMEAN (SE)[1]	Week 48 difference (95% CI)
4. Tremor at rest	0.28 (0.20)	0.02 (0.15)	-0.26 (-0.63; 0.11)
5. Action tremor	0.12 (0.30)	0.33 (0.23)	0.21 (-0.35; 0.77)
6. Increased tone	0.29 (0.30)	0.57 (0.23)	0.29 (-0.30; 0.87)
7. Rapid alternating movements of hands	1.04 (0.31)	0.49 (0.24)	-0.54 (-1.11; 0.02)
8. Finger taps	0.93 0.30	0.56 0.22	-0.37 (-0.97; 0.22)
9. Leg agility	1.00 0.31	0.58 0.23	-0.42 (-1.00; 0.16)
10. Heel-knee-shin test	0.43 0.31	0.61 0.23	0.18 (-0.39; 0.75)
11. Arising from chair	1.72 (0.55)	0.57 (0.41)	-1.15 (-2.17; -0.14)
12. Posture	0.92 (0.36)	0.26 (0.25)	-0.66 (-1.36; 0.03)
13. Body sway	1.31 (0.50)	0.42 (0.38)	-0.89 (-1.81; 0.03)
14. Gait	1.15 (0.28)	0.81 (0.21)	-0.34 (-0.83; 0.15)
[1] Mean estimated change-from-baseline (cfb) and standard error (SE) from the MMRM adjusted for baseline UMSARS, region and screening plasma NfL level.			

Summary table 4: Percentage change-from-baseline in Biomarkers: MRI and NfL at Week 48, Full analysis set (FAS) and by sub-groups

Biomarker Endpoints	Placebo: Week 48 cfb LSMEAN (SE)[1]	GM37v2 (Amlenetug): Week 48 cfb LSMEAN (SE)[1]	Week 48 difference (95% CI)
FAS (n=61; GM37v2(Amlenetug)/placebo=40/21)			
- MRI volumetric, Pons	-7.15 (1.14)	-5.27 (0.88)	1.88 (-0.49; 4.25)
- MRI volumetric, Cerebellum White matter	-10.69 (2.97)	-7.39 (2.57)	3.29 (-1.06; 7.65)
- MRI volumetric, Cerebellum Gray matter	-2.45 (1.04)	-3.92 (0.84)	-1.47 (-3.33; 0.40)
- NfL, CSF[2]	-4.41 (35.66)	-16.29 (23.76)	NA
Sub-group: MSA-C (n=42; GM37v2(Amlenetug)/placebo=30/12)			
- MRI volumetric, Pons	-7.37 (1.33)	-6.16 (0.98)	1.21 (-1.68; 4.10)
- MRI volumetric, Cerebellum White matter	-11.32 (2.91)	-7.51 (2.52)	3.81 (-1.05; 8.67)
- MRI volumetric, Cerebellum Gray matter	-3.89 (1.23)	-4.29 (0.97)	-0.40 (-2.75; 1.96)
- NfL, CSF[2]	-	-	-
Sub-group: UMSARS TS Baseline (BL) score < 40 (n=42; GM37v2(Amlenetug)/placebo=30/12)			
- MRI volumetric, Pons	-7.67 (1.44)	-5.31 (0.96)	2.36 (-0.72; 5.45)
- MRI volumetric, Cerebellum White matter	-10.92 (3.06)	-6.75 (2.44)	4.17 (-1.19; 9.53)
- MRI volumetric, Cerebellum Gray matter	-4.31 (1.31)	-3.90 (0.95)	0.41 (-2.10; 2.92)
- NfL, CSF[2]	-3.12 (49.73)	-14.38 (24.58)	NA
[1] Mean estimated percentage change-from-baseline (cfb) and standard error (SE) from the MMRM adjusted for baseline UMSARS, region and screening plasma NfL level. [2] percentage change-from-baseline in CSF NfL to Week 48 presented as mean (sd), n=31			

The results presented in summary table 4 shows a smaller regional volumetric reduction in the pons and cerebellar white matter at Week 48 in the active group compared to placebo

(see also figure 19). The neurofilament light chain CSF load indicated a smaller change from baseline in the active group compared to the placebo group (see also figure 20).

Safety of GM37v2 (Amlenetug):

The key safety results are summarized in the table below:

	Placebo		GM37v2	
	n	%	n	%
Number of Participants	21		40	
Participants with TEAEs	19	(90.5)	39	(97.5)
Participants with SAEs	7	(33.3)	12	(30.0)
Participants with TEAEs leading to Withdrawal	2	(9.5)	3	(7.5)
Deaths	2	(9.5)	2	(5.0)

These safety results indicate that the incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) were comparable between the GM37v2 (Amlenetug) treated patients and the placebo group. Furthermore, the anti-drug antibody prevalence was found to be 1/40 (2.5 %) and the anti-drug antibody incidence was zero in the active group.

EXPERIMENTAL SECTION – FORMULATION DEVELOPMENT FOR USE ACCORDING TO THE INVENTION

The pharmaceutical formulations of the present invention may be prepared and/or analysed and/or characterized by the methods such as analytical methods described below. These methods are all well known in the art of pharmaceutical sciences.

The examples and studies described below presents the work performed by to identify a clinically suitable pharmaceutical formulation comprising the antibody GM37 variant 2 (GM37v2).

Generalized description of analytical methods used in studies 1A, 1B and 1C presented below:

GP-HPLC

The gel permeation HPLC method was carried out on an Agilent 1200 HPLC system using a standardised TSK SWXL G3000 column. The mobile phase used was

0.2 M sodium phosphate at pH 7.0 at a flow rate of 1.0 mL/min. The sample injection volume was 50 uL. Protein loadings of approximately 250 ug were analysed using single determinations. The results were expressed to two decimal places as % monomer, % aggregate and % fragment in each sample.

Differential scanning calorimetry (DSC)

DSC was performed as per the instrument operating procedure. Samples were heated to 120°C and the melting temp measured to determine the formulation stability.

Dynamic Light Scattering (DLS)

DLS was performed as per the instrument operating procedure. DLS was used to determine the hydrodynamic radius of a sample by applying the Stokes-Einstein equation. The particles present in the sample created time dependent scattering of light, due to Brownian motion and the DLS monitors the light scatter using a high sensitivity detector.

Analysis was performed on the Viscoteck 802 DLS, with associated OmniSIZE 2.0 software. Samples were analysed in ten replicates.

Particulates

The absorbance of each sample at 340 nm and 620 nm was recorded as an indication of particulate levels and turbidity. Determinations were made singly using 1 mL of undiluted product. The product formulation buffer was used as a blank with the absorbance readings of the product taken at 340 nm and 620 nm by one operator only. Results were expressed to 3 decimal places.

Subvisible particle analysis

The particle counts were tested by light obscuration and the results reported according to the principals of USP<788> where required. 1 mL of sample was used as a wash through and discarded. Three readings were then taken using 1 mL of sample each and a cumulative result reported.

SDS-PAGE (reduced and non-reduced)

Analysis using Novex Pre-cast Minigels, SimplyBlue SafeStain and the Bio-Rad GS-800 Imaging Densitometer.

Samples were denatured by heating and treatment with sodium dodecyl sulphate. For reduced analysis, the disulphide bonds were disrupted with 2-mercaptoethanol. Polypeptides were separated on the basis of molecular size by electrophoresis through 4 % to 20 % gradient SDS PAGE gels. Following separation, the protein bands were visualised by SimplyBlueTM Safetstain (Coomassie Blue G-250). Polypeptide bands were quantified by

white light densitometry using the Bio-Rad GS-800 densitometer. The standard load mass was 3 ug (non-reducing) or 5 ug (reducing).

Example A - pH and Buffer Type of Formulations

Example A focuses on identifying the most favorable pH range and buffer type for GM37v2 formulations. Example A consists of two separate studies hereafter denoted Study 1A testing eight formulation candidates and Study 2A testing 16 formulation candidates.

Study 1A: pH and Buffer Type of Formulations

Eight formulation candidates, Formulation 1 to Formulation 8, were investigated and denoted F1-F8 (Table 1).

Table 1: Formulations investigated in study 1A of impact of pH/buffer type on GM37v2 formulations

pH Formulation ID	Formulation Buffer	pH of Formulation
F1	25 mM Sodium acetate	4.5
F2	25 mM Sodium acetate	5.0
F3	25 mM Sodium acetate	5.5
F4	25 mM Sodium citrate	6.0
F5	25 mM Histidine	6.0
F6	25 mM Sodium citrate	6.5
F7	25 mM Sodium phosphate	7.0
F8	25 mM Sodium phosphate	7.5
Control (SC)	PBS	7.4

The stability of GM37v2 was assessed in the eight formulation candidates at the target storage temperature 5°C ± 3 and at elevated temperature 40°C ± 2 at not more than 30% RH. The GM37v2 concentration in each formulation buffer was 30 mg/ml.

The stability of each formulation was measured by various well-known methods at baseline (Time zero, 0 weeks; T=0) and after one week (T=1, 1 week) for each formulation. Further, the stability study for each formulation included application of the following analytical methods (Table 2):

Table 2: Analytical methods to assess stability:

Analytical method	Time point		
	Time zero	1 week @ 5°C	1 week @ 40°C
GP-HPLC	X	X	X
DSC	X	X	X
DLS	X	X	X

GP-HPLC = Gel Permeation-High Performance Liquid Chromatography

DSC = Differential Scanning Calorimetry
DLS = Dynamic Light Scattering
The results of this stability study are summarized below.

Table 3: GP-HPLC - Percentage purity measured by amount of aggregate (%A), fragment (%F) and monomer (%M), results summary study 1A:

Formulations	Timepoint (weeks)								
	T=0			T=1					
				+5 ℃			+40 ℃		
	%M	%A	%F	%M	%A	%F	%M	%A	%F
F1	99.44	0.54	0.02	99.39	0.59	0.02	99.13	0.42	0.45
F2	99.40	0.58	0.02	99.45	0.53	0.02	99.31	0.52	0.17
F3	99.25	0.74	0.02	99.25	0.74	0.02	98.89	0.98	0.13
F4	99.25	0.74	0.01	99.25	0.74	0.02	99.00	0.89	0.12
F5	99.33	0.65	0.02	99.32	0.66	0.02	99.26	0.61	0.13
F6	99.21	0.77	0.02	99.22	0.76	0.02	98.81	1.07	0.12
F7	99.10	0.88	0.02	99.09	0.89	0.02	98.33	1.50	0.18
F8	99.06	0.92	0.02	99.02	0.96	0.02	98.15	1.64	0.21
Control	99.05	0.94	0.02	99.09	0.90	0.01	N/A	N/A	N/A
M = Monomer A = Aggregate F = Fragment N/A = Not Applicable									

• Initial aggregate level was pH dependent. Starting aggregate levels were higher at pH 7.5 and pH 7.0 in 25 mM sodium phosphate buffer (F8 (study 1A) and F7 (study 1A) respectively), compared to the other formulations at T=0 weeks. Aggregate levels were also higher in 25 mM sodium citrate buffers at pH 6.0 and pH 6.5 (F4 (study 1A) and F6 (study 1A), respectively) compared to the other formulations at T=0 weeks.

The formulation containing 25 mM sodium acetate buffer at pH 5.5 (F3, study 1A) also demonstrated higher aggregate levels at T=0 weeks compared to the other 25 mM sodium acetate buffer formulations (F1 (study 1A) and F2 (study 1A)). No marked difference in fragment levels at T=0 weeks was observed between formulations.

• All formulations demonstrated no marked change in % monomer, % aggregates and % fragments on storage at +5 °C for one week compared to their respective result at T=0 weeks.

• Aggregation at +40 °C was pH and buffer dependent.

• Formulations F7 (study 1A) and F8 (study 1A) (25 mM sodium phosphate at pH 7.0 and 7.5 respectively) demonstrated the highest increase in aggregates on storage at +40 °C for one week compared to their result at T=0 weeks. Formulation F6 (study 1A) (25 mM sodium citrate at pH 6.5), formulation F3 (study 1A) (25 mM sodium acetate at pH 5.5) and

formulation F4 (study 1A) (25 mM sodium citrate at pH 6.0), also demonstrated an increase in aggregates after one week at +40 °C but to a lesser extent than formulations F7 (study 1A) and F8 (study 1A).

- Formulations F1 (study 1A), F2 (study 1A) and F5 (study 1A) demonstrated no marked change in aggregate levels after storage at +40 °C for one week compared to their respective T= 0 weeks result.
- Formulation F1 (study 1A) (25 mM sodium acetate pH 4.5) demonstrated a marked change in fragment level after storage at +40 °C after one week compared to the T=0 weeks result from 0.02 % to 0.45 %.
- All other formulations demonstrated a slight increase in fragment levels (~0.1 %) after storage at +40 °C after one week compared to their respective T=0 weeks result.

By GP HPLC formulation F2 (study 1A) (25 mM sodium acetate buffer at pH 5.0) and formulation F5 (study 1A) (25 mM Histidine buffer at pH 6.0) presented as the most suitable formulation candidates for further development.

Thermal stability results summary study 1A

Table 4: DSC Differential Scanning Calorimetry

Formulation	Unfolding Events	Melting Temperature (℃)
		1d.p T=0
Formulation 1	Tm1	63.9
	Tm2	69.9
	Tm3	75.3
	Tm4	81.5
Formulation 2	Tm1	68.4
	Tm2	71.0
	Tm3	77.5
	Tm4	84.4
Formulation 3	Tm1	69.2
	Tm2	71.4
	Tm3	77.9
	Tm4	85.4
Formulation 4	Tm1	67.6
	Tm2	70.4
	Tm3	77.5
	Tm4	85.0
Formulation 5	Tm1	69.7
	Tm2	71.5
	Tm3	77.9
	Tm4	84.8
Formulation 6	Tm1	70.3
	Tm2	76.5
	Tm3	84.9
Formulation 7	Tm1	70.3
	Tm2	76.3
	Tm3	85.0
Formulation 8	Tm1	69.8
	Tm2	74.9
	Tm3	84.9
Study Control	Tm1	69.1
	Tm2	73.5
	Tm3	84.5

Tm1 = Melting temperature of unfolding event 1
Tm2 = Melting temperature of unfolding event 2
Tm3 = Melting temperature of unfolding event 3
Tm4 = Melting temperature of unfolding event 4

• Four unfolding events were observed for formulations F1 (study 1A), F2 (study 1A), F3 (study 1A), F4 (study 1A) and F5 (study 1A) at T=0 weeks. Three unfolding events were observed for formulations F6 (study 1A), F7 (study 1A) and F8 (study 1A).

• It is expected that the DSC profile for an IgG1 antibody will typically present three unfolding events. In this instance at low pHs between pH 4.5 to 6.0 a slightly more complex pattern was observed resulting in four unfolding events, which were not observed in the higher pH formulations between pH 6.5 to 7.5. This may have been due to different conformations of the product being stabilized at different pHs.

• Formulation F1 (study 1A) (25 mM sodium citrate at pH 4.5) had the lowest melting temperature for the first, second and third unfolding events at T=0 weeks.

• The formulations at pH 6.0 (F5, study 1A), pH 6.5 (F6, Study 1A) and pH 7.0 (F7, Study 1A), pH 7.5 (F8, Study 1A) had the highest melting temperatures at the first and second melting events detected in measurement.

• The melting temperature for all unfolding events was pH dependent. Melting temperature increased with pH from pH 4.5 to pH 7.5.

• By DSC pH 6.0, 6.5, 7.0 and 7.5 were concluded to demonstrate the highest predictive thermal stability.

High molecular weight species result summary study 1A

Table 5: Dynamic Light Scattering (DLS)

Formulations	Timepoint (weeks)					
	T=0		T=1			
			+5 ℃		+40 ℃	
	Rh (nm) by intensity	%RSD by intensity	Rh (nm) by intensity	%RSD by intensity	Rh (nm) by intensity	%RSD by intensity
F1	5.55	15.9	5.57	20.3	5.70	30.3
F2	5.47	17.0	5.65	22.0	5.82	23.3
F3	5.64	23.4	5.58	19.3	5.80	24.0
F4	5.94	24.0	5.81	23.2	5.86	24.4
F5	5.55	19.4	5.55	20.2	5.75	27.8
F6	5.87	22.6	5.78	19.9	5.76	20.0
F7	5.78	21.1	5.65	19.4	5.74	18.7
F8	5.88	25.6	5.81	21.5	5.98	24.9
SC	6.00	26.7	5.98	25.1	NA	NA

Rh = Hydrodynamic radius
%RSD = %Radial size distribution

- No high molecular weight species were detected in any of the formulations at T=0 weeks or after storage for one week at +5 °C and +40 °C.
- There was no marked difference between any of the formulations.

Study 2A: pH and Buffer type of Formulations

In a second part of Example A, Study 2A, 16 different formulation candidates were prepared, denoted formulation number 1-16, covering a pH range of 4 to 7 (Table 6). This study examined the effects of pH and buffer, as different buffers were used for a given formulation candidate. In addition, the GM37v2 concentration was varied from 25 mg/ml to 150 mg/ml. Finally, different tonicity modifiers/stabilizers were evaluated, including Arginine/Glutamate combinations, which have been shown to modulate viscosity at high protein concentrations. The actual pH values, GM37v2 concentrations, viscosities and osmolalities are listed in Table 7.

Table 6: Formulations investigated in study 2A (values in mg/mL for GM37v2 and in mM for excipients)

Form No	pH	acetate	citrate	His	phosphate	NaCl	sorbitol	Arg	Glu	GM37v2
1	4.0	20	0	0	0	140	0	0	0	25
2	4.0	20	0	0	0	0	270	0	0	50
3	5.0	20	0	0	0	0	270	0	0	50
4	5.0	0	0	20	0	0	0	100	100	25
5	5.5	0	20	0	0	0	270	0	0	50
6	5.5	0	0	20	0	70	130	0	0	100
7	6.0	0	20	0	0	0	0	50	50	100
8	6.0	0	0	0	20	0	0	100	100	150
9	6.0	0	0	20	0	140	0	0	0	50
10	6.5	0	20	0	0	0	130	50	50	50
11	6.5	0	0	0	20	140	0	0	0	100
12	6.5	0	0	20	0	0	0	100	100	150
13	7.0	0	0	0	20	0	270	0	0	100
14	7.0	0	0	20	0	70	0	50	50	150
15	5.5	0	0	10	0	70	0	50	50	150
16	5.5	0	0	40	0	70	130	0	0	50

Table 7: Viscosity and osmolality of the tested formulation candidates in study 2A

Form No.	Actual pH	Actual GM37v2	Osmolality	Viscosity
		mg/ml	mOmol/kg solvent	cP
1	4.00	24	293	1.07
2	4.44	47	301	1.60
3	5.12	53	314	1.56
4	5/02	22	231	1.29
5	5.59	53	340	1.51
6	5.58	103	311	2.22
7	6.00	102	288	2.34
8	6.05	154	280	3.97
9	6.03	54	307	1.44
10	6.57	53	158	1.42
11	6.49	107	305	2.21
12	6.56	155	274	4.26
13	6.99	109	358	2.52
14	6.98	145	305	3.85
15	5.54	149	296	3.78
16	5.52	49	331	1.37

Osmolality measurements

The osmolality of the solutions was measured using a freezing point depression instrument. The osmometer calibration is checked using the Clinitrol 290 (3MA029).

Viscosity measurements

The Viscosity was measured using an m-VROC™ Viscometer by Rheosense with an AlO chip. The shear rates employed are specified with the results. The viscometer was temperature controlled using a ThermoCube thermoelectric chiller and the samples were delivered using a

Hamilton 100 uL syringe (81060). The accuracy of the instrument was verified using neat Isopropyl alcohol and measured at 25°C.

Summary of viscosity results of study 2A

The viscosity values roughly were grouped by GM37v2 concentration. At ~25 mg/mL, the viscosity values averaged 1.2 cP. At 50 mg/mL or so, the values increased to ~1.5 cP. With GM37v2 concentrations near 100 mg/ml, the average value increased to ~2.3. Finally, at ~150 mg/mL, the viscosity values ranged from 3.8 to 4.3. These viscosity levels are quite low for formulations comprising a monoclonal antibody, especially at high antibody concentrations. Thus, the colloidal stability and propensity to self-associate appears to be quite low for GM37v2 in the tested formulation candidates. These data also indicated that clinically suitable high concentration formulations (> 200 mg/mL) could be possible for GM37v2 which were further investigated.

Size Exclusion Chromatography (SEC) measurements

SEC analysis was conducted on a Dionex UltiMate 3000 HPLC system equipped with a quaternary pump system and a variable wavelength detector. Briefly, the SE-HPLC method employs a Tosoh TSKgel G3000SWxL (#08541) HPLC column and a mobile phase of 50 mM sodium phosphate, 0.3 M sodium chloride, and pH of 7.0 with an isocratic flow at 1 mL/min with a column temperature of 20° C and a detection wavelength of 220 nm. System suitability was assessed for the SE-HPLC method for each sequence over the course of these studies. The %CV for chromatographic attributes of the main peak (MP) (retention time, Peak area, and relative area) are all less than 2% CV and the total relative areas sum to 100 %.

Cation exchange chromatography (CEX) measurements

CEX HPLC analysis was conducted on a Dionex UltiMate 3000 HPLC system equipped with a quaternary pump system and a variable wavelength detector. Briefly, the CEX HPLC method employs a Dionex MabPac SCX-10, 4 x 250 mm (#074625) HPLC column with a flow rate of 1.5 mL/min, a column temperature of 35° C and a detection wavelength of 220 nm. Samples for analysis were previously diluted to around 7 mg/mL in 0.2 M NaH_2P0_4. The gradient program for the CEX HPLC method uses a mobile phase A, B, and C. The gradient program is outlined below.

Mobile phase A: 20 mM sodium phosphate, 2 mM sodium chloride pH 5.8, 2.1 millisiemens.
Mobile phase B: 20 mM sodium phosphate, 2 mM sodium chloride, pH 8.0, 3.75 millisiemens.
Mobile phase C: 10 mM sodium phosphate, 1M sodium chloride, pH 6.0

Gradient conditions for CEX HPLC:

Time (min)	Mobile Phase A	Mobile Phase B	Mobile Phase C
0	100		
5	100		
6	60	40	
35		100	
45		100	
46			100
53			100
54	100		
65	100		

System suitability was assessed for the CEX HPLC method for each sequence over the course of these studies. The % CV for chromatographic attributes of the main peak (MP) (retention time, peak area, and relative area) are all less than 2% CV.

Summary of stability results of study 2A

The stability of the 16 formulation candidates was monitored using well known SEC and CEX chromatography techniques. T0 is baseline, T2 is 2 weeks and T4 is 4 weeks (Table 8 and 9).

Table 8: Stability of the tested formulation candidates were measured by Size-exclusion chromatography (SEC)

Form No.	Actual pH	Actual GM37v2	SEC t0	t2/5 C	t2/25 C	t2/40 C	t4/25 C	t4/40 C
		mg/ml						
1	4	24	99.47	99.44	99.24	90.60	96.84	85.18
2	4.44	47	99.46	99.53	99.50	97.75	99.44	96.27
3	5.12	53	99.45	99.47	99.44	98.04	99.40	97.09
4	5.2	22	99.49	99.50	99.48	97.79	99.40	96.48
5	5.59	53	99.39	99.38	99.31	97.85	99.20	96.85
6	5.58	103	99.38	99.35	99.28	97.76	99.17	96.63
7	6	102	99.28	99.33	99.24	97.81	99.16	96.86
8	6.05	154	99.35	99.30	99.19	97.69	99.07	96.60
9	6.03	54	99.38	99.35	99.31	97.90	99.22	96.88
10	6.57	53	99.33	99.30	99.23	97.80	99.13	96.86
11	6.49	107	99.17	99.08	98.84	97.05	98.64	95.89
12	6.56	155	99.33	99.25	99.15	97.05	99.02	96.46
13	6.99	109	99.10	98.94	98.66	96.42	98.40	94.88
14	6.98	145	99.28	99.17	99.02	97.35	98.86	96.07
15	5.54	149	99.38	99.33	99.24	97.68	99.13	96.55
16	5.52	49	99.45	99.43	99.40	97.93	99.35	96.85

Table 9: Stability of the tested formulation candidates were measured by Cation exchange chromatography (CEX)

Form No.	Actual pH	Actual GM37v2	CEX t0	t2/5 C	t2/25 C	t2/40 C	t4/25 C	t4/40 C
		mg/ml						
1	4.00	24	73.8	73.3	68.5	51.8	64.0	42.0
2	4.44	47	73.9	73.7	71.2	58.2	69.0	46.7
3	5.12	53	74.0	73.9	72.2	61.3	7.1	50.6
4	5.20	22	73.9	73.5	71.3	60.1	69.8	49.8
5	5.59	53	73.9	73.7	72.0	60.2	70.5	49.1
6	5.58	103	74.2	73.9	72.7	63.9	71.8	55.5
7	6.00	102	74.2	74.1	73.0	65.1	72.0	56.7
8	6.05	154	74.2	74.0	73.1	64.6	72.0	56.2
9	6.03	54	74.3	74.2	73.5	66.6	72.4	60.0
10	6.57	53	74.4	74.3	73.6	66.2	72.4	57.9
11	6.49	107	74.2	73.9	73.1	65.9	72.0	58.1
12	6.56	155	74.5	74.3	73.0	65.3	71.4	56.8
13	6.99	109	73.7	73.9	72.0	57.8	69.8	43.7
14	6.98	145	74.3	74.0	72.4	63.7	70.3	52.9
15	5.54	149	74.1	73.9	72.7	63.8	71.4	55.1
16	5.52	49	74.2	73.8	72.7	63.5	71.6	55.0

Formulation F1 ((study 2A), pH 4, acetate) demonstrated significant degradation at elevated temperature, especially after four weeks. In addition, Formulation F13 ((study 2A), pH 7, phosphate) also exhibited reduced stability compared to the other compositions. In the CEX test Formulation 2 ((study 2A), pH 4, acetate) also demonstrated signs of accelerated degradation at 40° C. The optimal pH appeared to be near 6, based on this SEC and CEX data.

Conclusion/summary of pH and buffer type studies

Study 1A:

Based on the range of well-established physical and chemical stability indicating methods described above in Example A study 1A, two buffer and pH pairs were found suitable to proceed into further formulation development and optimization.

The two buffer and pH pairs were:

F5 (study 1A) - about 25 mM histidine and pH around 6.0, and F2 (study 1A) - about 25 mM acetate and around pH 5.0.

Histidine (Formulation 5, Study 1A) demonstrated better stability than citrate at pH 6.0 due to an increase in aggregates observed by GP-HPLC with sodium citrate at pH 6.0 (Formulation 4, Study 1A).

pH 6.5 (Formulation 6, Study 1A) was deemed to be suitable from the visual analysis results but GP-HPLC indicated an increase in aggregates that was not seen at pH 5.0 (Formulation 2, Study 1A) and pH 6.0 (Formulation 5, Study 1A).

As stated above, the buffer ions selected for the further development were histidine at pH 6.0 and sodium acetate at pH 5.0. In addition to these most favored formulation candidates, a single formulation containing sodium citrate at pH 5.0 was also included in the further development.

Study 2A:

Collectively, the well-established physical and chemical stability indicating methods described above in Example A study 2A, indicate that optimal pH is likely near 5.5 to 6.0. The viscosity remains very low even at GM37v2 concentration of 150 mg/ml. The best buffer appears to be Histidine, given this pH range. Of the excipients tested, NaCl may have some protective effects against chemical degradation, but Arginine/Glutamate may also be useful for improving physical stability.

Example B - Excipients of Formulations

Example B focuses on identifying the most favorable excipients for the clinically acceptable formulation of GM37v2. Example B consists of 2 separate studies hereafter denoted Study 1B testing 11 formulation candidates and Study 2B testing 20 formulation candidates.

Study 1B: Excipients of Formulations

The stability of GM37v2 was assessed in 11 formulations comprising various excipients at the target storage temperature 5 ± 3°C and at elevated temperature 40 ± 2°C, as well as following agitation and freeze/thaw treatment. The GM37v2 concentration in each formulation was about 50 mg/mL.

The stability of each formulation was measured at baseline (Time zero, 0 months; T=0) and after one month (T=1, 1 month) for each formulation candidate.

Table 10: Formulations investigated in study 1B

Excipient Formulation ID	Formulation composition
F1	25 mM histidine, 50 mM sodium chloride, pH 6.0 + 200 mM glycine + 0.02 % Polysorbate 80
F2	25 mM histidine, 100 mM sodium chloride, pH 6.0 + 100 mM sucrose
F3	25 mM sodium acetate, 50 mM sodium chloride, pH 5.0 + 200 mM glycine

F4	25 mM sodium acetate, 50 mM sodium chloride, pH 5.0 + 200 mM glycine + 0.02 % Polysorbate 80
F5	25 mM sodium acetate, 50 mM sodium chloride, pH 5.0 + 100 mM arginine
F6	25 mM sodium acetate, 50 mM sodium chloride, pH 5.0 + 100 mM arginine + 0.02 % Polysorbate 80
F7	25 mM sodium acetate, 50 mM sodium chloride, pH 5.0 + 200 mM sucrose
F8	25 mM sodium acetate, 50 mM sodium chloride, pH 5.0 + 200 mM sucrose + 0.02 % Polysorbate 80
F9	25 mM sodium acetate, pH 5.0 + 180 mM arginine + 0.02 % Polysorbate 80
F10	25 mM sodium acetate, pH 5.0 + 250 mM glycine + 0.02 % Polysorbate 80
F11	25 mM sodium citrate, 50 mM sodium chloride, pH 5.0 + 200 mM glycine + 0.02 % Polysorbate 80
SC	Study control, PBS 7.4 pH

The stability study for each formulation included application of the following analytical methods:

Table 11: Analytical methods employed in study 1B:

Analytical method	Time point				
	Time zero	1 month @ 5°C	1 month @ 40°C	Agitation	Freeze/ thaw -70°C
GP-HPLC	X	X	X	X	X
Particulates A_{340}	X	X	X	X	X
Sub-visible particles	X	X	X	X	X
SDS-PAGE (non-reduced)	X	X	X	X	X
SDS-PAGE (reduced)	X	X	X	X	X
DSC	X	X	X	X	X
DLS	X	X	X	X	X

Agitation measurements:

The agitation protocol was initiated at T=0 months. Samples were agitated using a rotating agitator set to 30 rpm for 48 hours at +5 °C. Post agitation the samples were stored at +5 °C until testing.

Freeze/thaw measurements:

The freeze/thaw protocol was initiated at T=0 months. Samples were subjected to three freeze/thaw cycles consisting of approximately 18 hours at -70 °C followed by approximately 4-6 hours at room temperature. After freezing for the third time, the samples remained in the freezer until testing.

Stability results of study 1B summary:

Table 12: GP HPLC - Percentage purity

Timepoint		Data	Formulation										
			F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	SC
T=0	+5 ℃	% aggregates	0.85	0.72	0.70	0.82	0.70	0.82	0.69	0.83	0.82	0.76	0.81	1.03
		% monomer	99.13	99.26	99.28	99.16	99.27	99.16	99.28	99.15	99.16	99.22	99.17	98.96
		% fragment	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	+5 ℃ Agitation	% aggregates	0.83	0.72	0.71	0.80	0.69	0.81	0.71	0.82	0.82	0.76	0.80	
		% monomer	99.15	99.26	99.27	99.18	99.28	99.17	99.27	99.16	99.16	99.22	99.18	
		% fragment	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	
	-70 ℃ Freeze/thaw	% aggregates	0.86	0.74	0.73	0.88	0.70	0.81	0.72	0.84	0.82	3.05	0.81	
		% monomer	99.12	99.24	99.25	99.10	99.28	99.17	99.26	99.14	99.16	96.93	99.17	
		% fragment	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	
T=1M	+5 ℃	% aggregates	0.85	0.77	0.74	0.84	0.74	0.81	0.75	0.84	0.82	0.77	0.83	0.99
		% monomer	99.13	99.21	99.24	99.13	99.24	99.16	99.22	99.13	99.15	99.20	99.14	98.99
		% fragment	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
T=1M	+40 ℃	% aggregates	1.48	0.94	1.01	1.48	0.88	1.24	0.89	1.12	1.86	1.13	0.78	
		% monomer	97.54	98.19	97.74	97.15	97.05	96.49	97.69	97.52	95.85	97.83	97.09	
		% fragment	0.98	0.87	1.24	1.37	2.08	2.27	1.42	1.36	2.29	1.04	2.12	
		% aggregate change to T=0	0.63	0.22	0.31	0.66	0.18	0.42	0.20	0.29	1.04	0.37	-0.03	
		% monomer change to T=0	-1.59	-1.07	-1.54	-2.01	-2.22	-2.67	-1.59	-1.63	-3.31	-1.39	-2.08	
		% fragment change to T=0	0.98	0.87	1.24	1.37	2.08	2.27	1.42	1.36	2.29	1.04	2.12	

SC = Study control stored at -70 ℃ LOQ = Limit of quantitation (0.1 %)

• Low level of aggregate observed at T=0 months and after 1 month at +5 °C for all formulations.

• Fragment level <LOQ (0.01 %) was observed at T=0 months and after 1 month at +5 °C for all formulations.

• No change in any of the formulations for monomer purity, peak area or height after agitation at +5 °C

• No change in any of the formulations for monomer purity, peak area or height after freeze/thaw at -70 °C with the exception of F10 (study 1B). Aggregate level increased to 3.05 %. No change in fragment levels.

• At T=1 month formulations F1 (study 1B), F4 (study 1B), F6 (study 1B) and F9 (study 1B) demonstrated a marked change in % aggregates at +40 °C.

• At T=1 month all formulations demonstrated a marked change in % fragments at +40 °C with the highest percentage of fragments observed in formulations F5 (study 1B), F6 (study 1B), F9 (study 1B) and F11(study 1B).

• Formulations with PS80 (F4 (study 1B), F6 (study 1B), and F8 (study 1B)) were observed to have a higher percentage of aggregates versus formulation without PS80 (F3 (study 1B), F5 (study 1B) and F7 (study 1B)) at both T=0 month and T=1 month. However, F11 (study 1B) that also had PS80 demonstrated the lowest amount of aggregates at T=1 month stored at +40 °C.

• Sodium chloride has a positive effect on the level of aggregates (F3-F8 (study 1B) verses F9 (study 1B)).

• Arginine has a negative effect on the level of fragments (F5 (study 1B), F6 (study 1B) and F9 (study 1B)), however F11 (study 1B) which had no arginine also presented a high level of fragments.

• Citrate buffer has a positive effect on aggregate levels compared to acetate buffer at pH 5.0 (F11 (study 1B) versus F4 (study 1B)).

• Lowest amount of aggregates and fragments was seen in formulation F2 (study 1B) after storage at +40 °C for T=1 month.

Table 13: Particulates

Timepoint	Data	Formulation											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	SC
T=0	A340	0.108	0.111	0.115	0.107	0.114	0.102	0.116	0.097	0.096	0.092	0.112	0.223
	A620	0.008	0.012	0.014	0.010	0.011	0.007	0.016	0.006	0.007	0.029	0.010	0.028
T=0 +5 °C Agitation	A340	0.107	0.129	0.128	0.102	0.115	0.097	0.111	0.095	0.096	0.632	0.102	
	A620	0.008	0.017	0.017	0.008	0.012	0.006	0.013	0.005	0.006	0.026	0.007	
T=0 F/T	A340	0.256	0.117	0.112	0.098	0.108	0.102	0.111	0.093	0.097	0.636	0.100	
	A620	0.103	0.013	0.012	0.007	0.009	0.008	0.013	0.006	0.007	0.028	0.006	
T=1M (+5 °C)	A340	0.131	0.145	0.171	0.120	0.146	0.114	0.122	0.108	0.096	0.091	0.120	0.235
	A620	0.013	0.024	0.035	0.014	0.024	0.011	0.018	0.010	0.006	0.009	0.013	0.042
T=1M (+40 °C)	A340	0.369	0.218	0.185	0.267	0.176	0.193	0.159	0.209	0.261	0.241	0.302	
	A620	0.026	0.026	0.029	0.034	0.027	0.019	0.021	0.027	0.030	0.032	0.089	

SC = Study control F/T = Freeze Thaw

- At T=0 months A340 was higher in study control than the other formulations.
- F10 (study 1B) demonstrated a marked increase in A340 after agitation and freeze/thaw.
- F1 (study 1B) demonstrated a marked increase in A340 and A620 after agitation and freeze/thaw.
- F1 (study 1B), F2 (study 1B), F3 (study 1B) and F5 (study 1B) demonstrated a slight increase in A340 after storage at +5 °C for T=1 month.
- F1 (study 1B) and F11 (study 1B) demonstrated a marked increase in A340 after storage at +40 °C for T=1 month.
- F7 (study 1B) demonstrated the least change in A340 after storage at +40 °C for T=1 month.

Table 14: Sub-visible particles, T=0 (0 Months)

Formulation	Particle concentration [particles per container]			
	≥ 2 µm	≥ 5 µm	≥ 10 µm	≥ 25 µm
F1	1565	320	75	0
F2	3325	560	130	0
F3	6108	1228	265	10
F4	1758	365	145	10
F5	3805	840	193	3
F6	760	218	63	3
F7	5355	1100	280	5
F8	1228	238	75	3
F9	660	205	70	0
F10	525	155	43	3
F11	910	265	75	0

Table 15: Sub-visible particles, T=1 (1 Months)

Formulation	Particle concentration [particles per container]			
	≥ 2 µm	≥ 5 µm	≥ 10 µm	≥ 25 µm
F1	610	123	45	5
F2	975	173	50	3
F3	1835	385	85	10
F4	1103	195	45	0
F5	2940	538	143	18
F6	465	95	20	0
F7	1518	330	100	10
F8	793	193	90	13
F9	453	118	30	5
F10	430	118	8	0
F11	385	78	20	0

• At T=0 months the formulations that demonstrated the highest number of particles per container were F2 (study 1B), F3 (study 1B), F5 (study 1B) and F7 (study 1B).

• At T=1 month the formulations stored at +5 °C that demonstrated the highest number of particles per container were F3 (study 1B), F5 (study 1B), F7 (study 1B) and F8 (study 1B).

• At T=1 month the formulations stored at +5 °C that showed the lowest number of particles per container were F6 (study 1B), F10 (study 1B) and F11 (study 1B).

• Formulations containing PS80 demonstrated consistently lower SVP levels than those without.

• Formulation F2 (study 1B) is the only other formulation in the study without PS80, which displayed fewer sub-visible particles compared to F3 (study 1B), F5 (study 1B) and F7 (study

1B) at T=0 months and T=1 month, which indicates that pH 6.0 may be more suitable than pH 5.0.

Table 16: SDS PAGE (non-reduced) – Number of bands detected visually

Timepoint	Temperature	Formulation											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	SC
T=0	+5 °C	6	6	6	6	6	6	6	6	6	6	6	6
	+5 °C Agitation	6	6	6	6	6	6	6	6	6	6	6	
	-70 °C Freeze-thaw	6	6	6	6	6	6	6	6	6	6	6	
T=1M	+5 °C	6	6	6	6	6	6	6	6	6	6	6	6
	+40 °C	8	8	8	9	11	11	9	9	10	8	8	

SC = Study control stored at -70 °C

• No differences observed in band number between formulations at T=0 months.

• After 1 month stored at +5 °C no change in band number was noted for any of the formulations.

• After 1 month stored at +40 °C additional fragment bands were observed in all formulations.

• The greatest number of additional bands were observed in formulations F5 (study 1B), F6 (study 1B) and F9 (study 1B) after 1 month stored at +40 °C. F5 (study 1B), F6 (study 1B) and F9 (study 1B) are all formulated with arginine.

• No changes observed in band number for all formulations and after agitation or freeze/thaw.

Table 17: SDS PAGE (reduced) – Percentage Purity - Relative percentage of IgG band area as heavy and light chain bands

Timepoint	Temperature		Formulation										
			F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	SC
T=0	+5 °C		99.0	98.9	99.0	98.9	99.0	99.1	99.0	98.9	99.0	99.0	98.9	98.8
	+5 °C Agitation		98.9	99.1	99.0	99.1	99.1	99.1	99.0	99.1	99.1	99.0	98.9	
	-70 °C Freeze-thaw		99.0	98.8	98.9	98.9	99.0	99.0	99.0	99.0	99.0	98.9	99.0	
T=1M	+5 °C		98.8	98.5	98.9	98.9	98.6	98.3	98.7	98.7	98.8	98.7	98.3	
	+40 °C		97.2	98.0	96.4	94.2	93.3	92.1	96.7	95.2	96.8	96.1	95.7	98.0

SC = Study control stored at -70 °C

• No marked differences observed between formulations at T=0 months.

• After 1 month stored at +5 °C no marked change in percentage purity was noted for any of the formulations.

• After 1 month stored at +40 °C additional fragment and high molecular weight bands were observed in all formulations with a corresponding slight decrease in percentage IgG purity.

• The greatest decrease in purity was observed in formulations F4 (study 1B), F5 (study 1B), F6 (study 1B) and F9 (study 1B) at one month stored at +40 °C. F5 (study 1B), F6 (study 1B) and F9 (study 1B) are all formulated with arginine.

• Formulation F2 (study 1B) at one month stored at +40 °C, demonstrated the smallest change in purity compared to the study start.

• No marked changes in reduced SDS PAGE results observed in all formulations after agitation or freeze/thaw.

Table 18: DSC – Thermal stability

Timepoint	Melting Temperature	Formulation										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	SC
T=0	Tm_1 (°C)	70.10	69.34	69.71	69.58	67.39	67.37	69.90	69.82	66.97	71.42	68.95	68.83
	Tm_2 (°C)	76.71	76.51	76.51	76.75	74.83	74.66	76.95	77.13	74.50	77.90	75.35	72.48
	Tm_3 (°C)	83.54	83.52	83.12	83.34	81.32	81.41	83.38	83.81	80.93	83.90	81.83	83.95

Tm_1 = Melting temperature of unfolding event 1
Tm_2 = Melting temperature of unfolding event 2
Tm_3 = Melting temperature of unfolding event 3

• Three melting temperatures were observed for all formulations at T=0 months, consistent for an IgG molecule.

• Formulation F5 (study 1B), F6 (study 1B) and F9 (study 1B) had the lowest temperature unfolding event at T=0 months and all are formulated with arginine.

• Formulations F1 (study 1B) and F10 (study 1B) had the highest melting temperatures at T=0 months (70.10 °C and 71.42 °C, respectively).

Table 19: DLS - high molecular weight species

Timepoint	Data	Formulation											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	SC
T=0M	Rh (nm) by intensity	5.91	6.33	6.14	6.07	6.22	6.54	7.58	7.04	6.80	5.99	6.42	5.97
	%RSD by intensity	27.3	26.0	28.4	27.7	29.7	31.3	37.3	28.7	29.0	30.3	32.8	30.9
T=0 Agitation	Rh (nm) by intensity	5.51	6.48	6.17	5.71	6.38	7.74 401.63	7.32	6.18 668.95	6.98	6.13	5.98	
	%RSD by intensity	20.3	28.2	31.1	22.8	28.4	40.7 48.4	34.4	30.5 42.4	29.9	31.6	25.7	
T=0 F/T	Rh (nm) by intensity	5.68 310.37	6.66	6.40	6.20	6.52	6.24	7.60	6.80 359.07	6.66	6.08	6.52	
	%RSD by intensity	24.1 25.7	33.1	36.9	33.1	33.5	26.4	36.6	27.6 27.1	28.1	29.1	33.3	
T=1M (+5 °C)	Rh (nm) by intensity	5.97	6.27	6.20	6.28	6.29	6.23	7.26	7.02	6.93	5.74	5.88	6.18
	%RSD by intensity	27.0	22.9	35.0	34.3	32.1	28.9	30.3	30.1	34.4	27.2	27.9	37.8
T=1M (+40 °C)	Rh (nm) by intensity	7.53 100.52	6.48	6.25	6.23 98.42	6.47	6.60	7.66	7.75 406.96	6.97	6.50 118.08	6.40 390.93	
	%RSD by intensity	56.0 61.6	30.8	35.1	34.8 45.5	35.9	37.2	39.1	39.7 53.9	31.5	38.7 46.3	35.1 47.8	

Rh = Hydrodynamic radius RSD = Relative standard deviation

• No high molecular weight species were observed in any formulation at T=0 months and T=1 month stored at +5 °C.

• Higher molecular species were detected in formulations F1 (study 1B), F4 (study 1B), F8 (study 1B), F10 (study 1B) and F11 (study 1B) after one month at +40 °C. F1 (study 1B), F4 (study 1B), F10 (study 1B) and F11 (study 1B) are all formulated with glycine.

• Higher molecular weight species observed in formulations F1 (study 1B) and F8 (study 1B) after freeze/thaw.

• Higher molecular weight species observed in formulations F6 (study 1B) and F8 (study 1B) after agitation.

Study 2B: Excipients of Formulations

Twenty different compositions were evaluated in Study 2B, all at GM37v2 concentrations targeted to be 225 mg/mL. This concentration was selected based on the low viscosity observed for the formulations tested in Study 2A. The actual GM37v2 concentrations ranged from about 216 mg/mL to 233 mg/mL. The pH range covered from 5.1 to 6.4. The measured viscosities were consistently very low, ranging from 10.1 to 16.2 cP.

Table 20: Formulations investigated in Study 2B

Formulation	Buffer type	Buffer conc.	pH	Excipient	GM37v2 (mg/mL)
1	Acetate	20	5.0	100 mM Arginine/100 mM Glutamate	225
2	Acetate	20	5.5	100 mM Arginine/100 mM Glutamate	225
3	Acetate	20	5.8	100 mM Arginine/100 mM Glutamate	225
4	Histidine	40	5.0	100 mM Arginine/100 mM Glutamate	225
5	Histidine	20	5.5	100 mM Arginine/100 mM Glutamate	225
6	Histidine	20	5.8	100 mM Arginine/100 mM Glutamate	225
7	Acetate	10	5.5	100 mM Arginine/100 mM Glutamate	225
8	Acetate	40	5.5	100 mM Arginine/100 mM Glutamate	225
9	Acetate	20	5.0	140 mM NaCl	225
10	Acetate	20	5.5	140 mM NaCl	225
11	Acetate	20	5.8	140 mM NaCl	225
12	Histidine	20	5.0	140 mM NaCl	225
13	Histidine	40	5.5	140 mM NaCl	225
14	Histidine	20	5.8	140 mM NaCl	225
15	Acetate	20	5.0	70 mM NaCl, 50 mM Arginine/ 50 mM Glutamate	225
16	Acetate	20	5.5	70 mM NaCl, 50 mM Arginine/ 50 mM Glutamate	225
17	Acetate	20	5.8	70 mM NaCl, 50 mM Arginine/ 50 mM Glutamate	225
18	Histidine	20	5.0	70 mM NaCl, 50 mM Arginine/ 50 mM Glutamate	225
19	Histidine	20	5.5	70 mM NaCl, 50 mM Arginine/ 50 mM Glutamate	225
20	Histidine	40	5.8	70 mM NaCl, 50 mM Arginine/ 50 mM Glutamate	225

Table 21: Viscosity and osmolality of the tested formulation candidates in Study 2B

Formulation	Acetate (mM)	Histidine (mM)	Arginine/Glutamate	NaCl	pH sample	Osmo sample (mOsm/kg*H20)	GM37v2 (mg/mL)	Viscosity (cP)
F01	20		100		5.2	348	223.9	11.49
F02	20		100		5.6	359	225.7	13.51
F03	20		100		6.1	334	216.5	12.02
F04		40	100		5.1	403	218.2	12.11
F05		20	100		5.7	351	235.1	13.46
F06		20	100		6.3	335	225.6	14.02
F07	10		100		5.6	402	229.7	11.68
F08	40		100		5.7	364	234.3	13.52
F09	20			140	5.4	432	234.9	14.56
F10	20			140	5.8	404	219.5	10.79
F11	20			140	6.2	405	229.0	12.58
F12		20		140	5.5	410	219.5	10.77
F13		40		140	5.8	472	221.7	14.50
F14		20		140	6.4	402	224.5	11.61
F15	20		50	70	5.3	372	215.4	10.09
F16	20		50	70	5.7	383	219.9	11.61
F17	20		50	70	6.2	379	217.7	15.20
F18		20	50	70	5.3	386	233.4	16.21
F19		20	50	70	5.8	335	218.8	12.11
F20		40	50	70	6.2	408	222.2	13.07

Summary of stability results of study 2B

The monomer content (or percent of the main peak, MP) at T0 weeks and various time points and temperatures is tabulated in Table 22. The initial samples display monomer contents at 99.0-99.3%, with a small amount of dimer and fragment present. There was little if any changes over four weeks when stored at 5° C and small decreases upon storage at 25° C for the same length of time. At 40° C, the monomer content drops to about 96% after four weeks. These losses were mostly due to an increase in dimer and HMW aggregate, with only small changes in the amount of fragmentation.

Table 22: Stability of the tested formulation candidates were measured by Size-exclusion chromatography (SEC)

Form No	pH sample	Starting GM37v2 (mg/mL)	SEC T0 MP	SEC T2wk 5C MP	SEC T2wk 25C MP	SEC T2wk 40C MP	SEC T4wk 5C MP	SEC T4wk 25C MP	SEC T4wk 40C MP
F01	5.2	223.9	99.3	99.2	99.1	97.0	99.2	99.0	95.9
F02	5.6	225.7	99.2	99.2	99.1	97.1	99.2	99.0	96.2
F03	6.1	216.5	99.2	99.2	99.0	97.0	99.1	98.9	96.2
F04	5.1	218.2	99.3	99.3	99.2	96.9	99.3	99.1	95.7
F05	5.7	235.1	99.3	99.2	99.1	97.2	99.2	99.0	96.2
F06	6.3	225.6	99.2	99.1	99.0	97.0	99.1	98.9	96.1
F07	5.6	229.7	99.2	99.2	99.1	97.1	99.2	99.0	96.2
F08	5.7	234.3	99.2	99.2	99.0	97.1	99.1	98.9	96.2
F09	5.4	234.9	99.1	99.0	98.8	96.5	99.0	98.7	95.2
F10	5.8	219.5	99.0	99.0	98.7	96.5	98.9	98.6	95.5
F11	6.2	229.0	99.0	98.9	98.6	96.5	98.8	98.5	95.4
F12	5.5	219.5	99.2	99.2	99.0	96.9	99.2	98.9	95.8
F13	5.8	221.7	99.2	99.2	99.0	96.9	99.2	98.9	95.8
F14	6.4	224.5	99.1	99.0	98.8	96.7	99.0	98.6	95.6
F15	5.3	215.4	99.2	99.1	99.1	96.8	99.2	99.0	95.6
F16	5.7	219.9	99.2	99.1	99.0	96.9	99.1	98.9	95.9
F17	6.2	217.7	99.1	99.1	98.9	96.9	99.0	98.8	95.9
F18	5.3	233.4	99.3	99.2	99.1	97.0	99.2	99.0	95.8
F19	5.8	218.8	99.2	99.2	99.1	97.1	99.2	99.0	96.1
F20	6.2	222.2	99.2	99.1	99.0	97.0	99.1	98.9	96.0

The relative area of the main peak (MP) at T0 weeks and various time points and temperatures is tabulated in Table 23. The main peak was initially about 74% or the relative area of the chromatogram. There is little, if any, change during storage at 5° C. However, at 25° C, there is an appreciable decrease to ~ 71% after four weeks and 50-60% when stored at 40° C for that length of time. So, even at these very high GM37v2 concentrations, the formulations appear to be chemically and physically stable when stored at 5° C and even at elevated temperatures, the losses are quite modest.

Table 23: Stability of the tested formulation candidates were measured by Cation exchange chromatography (CEX)

"m" means that no data is available for this data point

Form No	pH sample	Starting GM37v2 (mg/mL)	CEX T0 MP	CEX T2wk 5C MP	CEX T2wk 25C MP	CEX T2wk 40C MP	CEX T4wk 5C MP	CEX T4wk 25C MP	CEX T4wk 40C MP
F01	5.2	223.9	73.9	73.5	71.6	60.5	73.6	70.6	51.8
F02	5.6	225.7	73.9	74.0	72.4	62.9	73.9	71.6	55.3
F03	6.1	216.5	74.1	73.8	73.0	65.2	74.1	72.4	58.9
F04	5.1	218.2	73.8	73.4	71.4	60.2	73.4	70.3	51.9
F05	5.7	235.1	74.0	73.8	72.4	63.3	73.9	71.8	m
F06	6.3	225.6	74.2	74.1	72.8	65.5	74.0	m	59.2
F07	5.6	229.7	73.9	73.6	72.4	62.7	73.7	71.5	55.5
F08	5.7	234.3	74.1	73.7	72.6	63.6	73.8	72.1	56.2
F09	5.4	234.9	73.9	73.5	72.0	62.1	73.6	71.2	54.5
F10	5.8	219.5	73.9	73.9	72.6	64.5	73.9	71.9	58.1
F11	6.2	229.0	74.0	73.8	72.7	66.4	74.0	72.7	60.9
F12	5.5	219.5	73.8	73.6	72.2	64.1	73.6	71.6	57.7
F13	5.8	221.7	73.9	73.8	72.4	64.8	73.8	72.4	59.0
F14	6.4	224.5	74.1	73.9	72.6	66.9	74.0	72.4	61.8
F15	5.3	215.4	73.7	73.5	72.0	61.6	m	71.8	53.4
F16	5.7	219.9	73.9	73.8	72.6	64.1	74.1	71.7	59.2
F17	6.2	217.7	74.0	73.8	72.9	66.0	73.9	m	59.9
F18	5.3	233.4	73.9	73.5	71.9	62.6	73.6	71.0	55.0
F19	5.8	218.8	73.9	73.7	72.7	64.9	m	72.0	60.3
F20	6.2	222.2	74.2	73.8	72.7	66.0	74.1	72.0	59.5

Conclusion/summary of excipient study

Study 1B:

Based on the of all analytical methods described in Study 1B the most suitable formulation candidates are formulations F2 (study 1B) and F3 (study 1B).

The data was assessed for each formulation; however, trends were also assessed across formulations by identifying consistent effects for specific excipients.

Formulation F3 (study 1B) presented more sub-visible particles at both the study start and T=1 month when stored at +5 °C, compared to formulation F2 (study 1B).

On comparison of all the formulations the presence of PS80 reduced the overall number of sub-visible particles and to a lesser extent the number of visible particles. Formulation F4 (study 1B) which differ from composition as F3 (study 1B) by the presence of 0.02% PS80 is not preferred as formulation candidate as although it had less sub-visible particles than F3

(study 1B), it also demonstrated lower purity by SDS PAGE and GP HPLC and presence of aggregates by DLS and particulates determined at A340.

The most promising formulation candidate is therefore formulation F2 (study 1B) (25 mM Histidine, 100 mM Sodium Chloride, pH 6.0 and 100 mM sucrose). The rationale for selecting this candidate to be best suited for further development was that overall the data for F2 (study 1B) was most favorable since it generally demonstrated the least amount of change across all assays.

Study 2B:

The SEC data indicate that the stability is best at pH 4.5 and 6.5, depending on the storage temperature. Histidine buffer can be stabilizing especially at concentrations > 20 mM. NaCl has only a minor effect on stability. Higher GM37v2 concentration leads to more rapid loss of monomer, presumably by aggregation, but losses are small over the time course studied. The CEX data indicate that maintaining the relative amount of the pain peak is best at pH 5.5 to 7.0. Again, Histidine is favorable for maintaining stability. NaCl can also be beneficial up to around 100 mM.

Given these collective findings, the optimal pH is likely to be near 6.0, using a Histidine buffer concentration of 20-40 mM. The nature of the tonicity modifier does not appear to be critical for obtaining a suitable clinical formulation, but NaCl seems to be the best of those tested in Study 2B.

Example C – Surfactants of Formulations

Finally, the effect of adding polysorbate 80 to the most promising formulation candidates obtained from Example A and Example B was investigated.

Study 1C: Non-ionic Surfactants (Polysorbate 80)

The stability of GM37v2 was assessed in two identical formulations, except that one formulation comprised polysorbate 80 (F2 (study 1C)) and one did no (F1 (study 1C)), otherwise the excipients were identical. The formulations were tested at the target storage temperature 5 ± 3°C and at elevated temperature 40 ± 2°C at not more than 25% RH, as well as following agitation. The GM37v2 concentration in each formulation was of 50.0 mg/mL +/- 5.0.

Table 24: Formulations investigated in study 1C

Polysorbate 80 Formulation ID	Formulation composition
F1	25 mM L-histidine, 100 mM NaCl, 100 mM sucrose, pH 6.0
F2	25 mM L-histidine, 100 mM NaCl, 100 mM sucrose, pH 6.0 + 0.02% Polysorbate 80

Both formulations were subject to an agitation protocol, which was initiated at T=0 months. Samples were agitated using a rotating agitator set to 30 rpm for 48 hours at +5 °C. Post agitation the samples were stored at +5 °C until testing.

The stability of each of the two formulations were then measured at baseline (Time zero, 0 months; T=0), after three months (T=3, 3 months) and after 6 months (T=6, 6 months) as described in table 25.

Table 25: Analytical methods used in Study 1C

Analytical method	Time point (month) at 5°C and 40°C			
	0	3	6	Agitation*
Visual appear-ance (particles)	x	x	x	x
Non-reduced CE-SDS	X	X	X	X
Reduced CE-SDS	x	x	x	x
GP-HPLC	X	x	x	X
Sub.visible particle**	x	x	x	x

*Agitation study performed over 48 hours at 5°C on a rotatry shaker at time zero only.
** the analysis was only performed at 5°C

Summarized results of study 1C:

Table 26: Storage at +5°C without tween

Assay	Specification	Timepoint (Months) / Testing Window (Dates of Initiation to Last Assay)		
		0	3	6
		16Jan17 to 23Jan17	17Apr17 to 20APR17	17Jul17 to 26Jul17
Visible particles	Report result	FVP	FVP	FVP
Reduced CE SDS	≥95.0 % IgG as heavy and light chains	98.8	98.7	98.8
Non-reduced CE SDS	Report result as % intact IgG and comparison to reference standard	97.9	97.2	97.4
GP HPLC	≥95.0 % IgG monomer	99.5	99.4	99.4
	≤5.0 % aggregates	0.5	0.6	0.6
	Report % fragments	<LOQ	<LOQ	<LOQ
Sub-visible particle counting	Pass according to USP<788>			
	≥25 µm: ≤600 particles per vial	285	53	767
	≥10 µm: ≤6000 particles per vial	20892	4884	13736
	≥5 µm: Report particles per vial	84719	30690	73010
	≥2 µm: Report particles per vial	266894	117471	233688

FVP = Free from visible particles CR = Comparable to reference <LOQ = less than limit of quantitation for the method (<0.1 %)

Table 27: Storage at +5°C with tween

Assay	Specification	Timepoint (Months) / Testing Window (Dates of Initiation to Last Assay)		
		0	3	6
		16Jan17 to 23Jan17	17Apr17 to 20Apr17	17Jul17 to 26Jul17
Visible particles	Report result	FFP	FFP	FVP
Reduced CE SDS	≥95.0 % IgG as heavy and light chains	98.9	98.7	98.8
Non-reduced CE SDS	Report result as % intact IgG and comparison to reference standard	97.9	97.7	97.3
GP HPLC	≥95.0 % IgG monomer	99.5	99.4	99.3
	≤5.0 % aggregates	0.5	0.6	0.6
	Report % fragments	<LOQ	<LOQ	<LOQ
Sub-visible particle counting	Pass according to USP<788>			
	≥25 µm: ≤600 particles per vial	19	12	16
	≥10 µm: ≤6000 particles per vial	401	273	233
	≥5 µm: Report particles per vial	1909	1573	1306
	≥2 µm: Report particles per vial	12534	10388	8764

FFP = Few fibrous particles FVP = Free from visible particles CR = Comparable to reference <LOQ = less than limit of quantitation for the method (<0.1 %)

Table 28: Storage at +5°C agitation without tween

Assay	Specification	Timepoint (Months) / Testing Window (Dates of Initiation to Last Assay)	
		Agitation at T=0	
		16Jan17 to 23Jan17	
Visible particles	Report result	NR	
Reduced CE SDS	≥95.0 % IgG as heavy and light chains	98.8	
Non-reduced CE SDS	Report result as % intact IgG and comparison to reference standard	97.8	
		CR	
GP HPLC	≥95.0 % IgG monomer	99.4	
	≤5.0 % aggregates	0.6	
	Report % fragments	<LOQ	
Sub-visible particle counting	Pass according to USP<788>		
	≥25 µm: ≤600 particles per vial	13	
	≥10 µm: ≤6000 particles per vial	1000	
	≥5 µm: Report particles per vial	28190	
	≥2 µm: Report particles per vial	123465	

NR = No result (was not possible to assess visible particles due to sample being opaque) CR = Comparable to reference
<LOQ = less than limit of quantitation for the method (<0.1 %)

Table 29: Storage at +5°C agitation with tween

Assay	Specification	Timepoint (Months) / Testing Window (Dates of Initiation to Last Assay)	
		Agitation at T=0	
		16Jan17 to 23Jan17	
Visible particles	Report result	FVP	
Reduced CE SDS	≥95.0 % IgG as heavy and light chains	98.9	
Non-reduced CE SDS	Report result as % intact IgG and comparison to reference standard	97.9	
		CR	
GP HPLC	≥95.0 % IgG monomer	99.5	
	≤5.0 % aggregates	0.5	
	Report % fragments	<LOQ	
Sub-visible particle counting	Pass according to USP<788>		
	≥25 µm: ≤600 particles per vial	3	
	≥10 µm: ≤6000 particles per vial	253	
	≥5 µm: Report particles per vial	978	
	≥2 µm: Report particles per vial	3893	

FVP = Free from visible particles CR = Comparable to reference <LOQ = less than limit of quantitation for the method (<0.1 %)

Table 30: Storage at +40°C without tween

Assay	Specification	Timepoint (Months) / Testing Window (Dates of Initiation to Last Assay)		
		0	3	6
		16Jan17 to 23Jan17	17Apr17 to 20Apr17	17Jul17 to 26Jul17
Visible particles	Report result	FVP	FFP	FFP
Reduced CE SDS	≥95.0 % IgG as heavy and light chains	98.8	94.2	90.4
Non-reduced CE SDS	Report result as % intact IgG and comparison to reference standard	97.9	90.3	84.0
		CR	CR	NCR
GP HPLC	≥95.0 % IgG monomer	99.5	96.5	92.1
	<5.0 % aggregates	0.5	1.4	3.2
	Report % fragments	<LOQ	2.1	4.7
Sub-visible particle counting	Pass according to USP<788>			
	≥25 µm: <600 particles per vial	285		
	≥10 µm: ≤6000 particles per vial	20892	NT	NT
	≥5 µm: Report particles per vial	84719		
	≥2 µm: Report particles per vial	266894		
FVP – Free from visible particles NT = Not tested	FFP – Few fibrous particles <LOQ = Less than limit of quantitation for the method (<0.1 %)	CR – Comparable to reference	NCR – Not comparable to reference	

Table 31: Storage at +40°C with tween

Assay	Specification	Timepoint (Months) / Testing Window (Dates of Initiation to Last Assay)		
		0	3	6
		16Jan17 to 23Jan17	17Apr17 to 20Apr17	17Jul17 to 26Jul17
Visible particles	Report result	FFP	FVP	FFP
Reduced CE SDS	≥95.0 % IgG as heavy and light chains	98.9	94.1	90.3
Non-reduced CE SDS	Report result as % intact IgG and comparison to reference standard	97.9	90.5	84.0
		CR	CR	CR
GP HPLC	≥95.0 % IgG monomer	99.5	96.4	91.9
	≤5.0 % aggregates	0.5	1.5	3.4
	Report % fragments	<LOQ	2.1	4.7
Sub-visible particle counting	Pass according to USP<788>			
	≥25 µm: ≤600 particles per vial	19	NT	NT
	≥10 µm: ≤6000 particles per vial	401		
	≥5 µm: Report particles per vial	1909		
	≥2 µm: Report particles per vial	12534		

FFP = Few fibrous particles FVP = Free from visible particles CR = Comparable to reference NT = Not Tested

<LOQ = less than limit of quantitation for the method (<0.1 %)

The formulation without Polysorbate 80 presented more sub-visible particles of all sizes at both the study start and T=6 months when stored at +5°C compared to the formulation with Polysorbate 80, but both formulations demonstrated no marked change at T=6 compared to their respective T=0 months results.

The formulations, with and without Polysorbate 80, stored at +5 °C were both free from visible particles at T=6 months and demonstrated no marked change by GP HPLC, reduced and non-reduced CE SDS at T=6 months compared to the T=0 months measurements.

At six months, the formulations (with and without Polysorbate 80) at the +40 °C condition were determined to have no marked difference between them. However, at six months both these formulations demonstrated a comparable trend of decreasing percentage IgG monomer with concomitant increases in percentage aggregates and fragments by GP HPLC and decreasing purity by reduced and non-reduced CE SDS compared to the study start.

For the formulations subject to the agitation protocol, it was found that the formulation without Polysorbate 80 presented more sub-visible particles of all sizes compared to the formulation with polysorbate 80.

Study 2C: Non-ionic Surfactants (Polysorbate 80 / Poloxamer 188)

The effect of adding a surfactant to the most promising formulations candidates obtained from studies 2A and 2B was investigated.

Ten formulations were tested, and their composition is described in table 32.

Table 32: Formulations investigated in study 2C

Formulations	Base composition	Surfactant
*F01	20 mM Histidine, 140 mM NaCl, pH 6.0, 225 mg/mL GM37v2	None
F02	20 mM Histidine, 140 mM NaCl, pH 6.0, 225 mg/mL GM37v2	0.02% (w/v) PS80
F03	20 mM Histidine, 140 mM NaCl, pH 6.0, 225 mg/mL GM37v2	0.05% (w/v) PS80
F04	20 mM Histidine, 140 mM NaCl, pH 6.0, 225 mg/mL GM37v2	0.02% (w/v) Poloxamer 188
*F05	20 mM Histidine, 140 mM NaCl, pH 6.0, 225 mg/mL GM37v2	0.05% (w/v) Polaxamer 188
*F06	20 mM Acetate, 70 mM NaCl, 50 mM Arginine/Glutamate, pH 6.0, 225 mg/mL GM37v2	None
F07	20 mM Acetate, 70 mM NaCl, 50 mM Arginine/Glutamate, pH 6.0, 225mg/mL GM37v2	0.02% (w/v) PS80
F08	20 mM Acetate, 70 mM NaCl, 50 mM Arginine/Glutamate, pH 6.0, 225 mg/mL GM37v2	0.05% (w/v) PS80
F09	20 mM Acetate, 70 mM NaCl, 50 mM Arginine/Glutamate, pH 6.0, 225 mg/mL GM37v2	0.02% (w/v) Poloxamer 188
*F10	20 mM Acetate, 70 mM NaCl, 50 mM Arginine/Glutamate, pH 6.0, 225 mg/mL GM37v2	0.05% (w/v) Polaxamer 188
*CTL	25 mM Histidine, 100 mM NaCl, 100 mM Sucrose, 50 mg/mL, pH 6.0	0.02% (w/v) PS80

* Subvisible particle count was measured on these formulations only

These formulations were separately exposed to multiple freeze-thaw cycles and agitation stress. These formulations were tested by A280, SE-HPLC, and sub-visible particle analysis (select samples).

Agitation stress measurements in study 2C

Formulations were filled into Schott, Fiolax, clear blowback, type I glass stoppered with Flurotec serum stoppers (Target of 1 mL in a 2 mL vial) and sealed with crimp caps. These vials were oriented in a horizontal position and agitated at room temperature using an orbital shaker (3 mm orbit) at a speed of 590 rpm (revolutions/minute). Samples were taken at 5-hours and 24-hours and tested. Non-agitated control samples were kept in a sample box at room temperature.

5 times (5x) Freeze-thaw stress measurements in study 2C

Formulations were filled (0.65 mL) into polypropylene tubes and exposed to 5x freeze-thaw cycles. Samples were frozen at -80° C for at least 12-hours. During the thaw, the tubes were placed at room temperature and allowed to thaw for no longer than 3-hours. All of the thawed formulations were inverted several times to mix, prior to re-freezing. After the 5x freeze-thaw cycles, the samples were analyzed.

Summarized results of study 2C:

The agitation stress experiment showed that there was no significant variation in the measured GM37v2 concentration between any formulation candidates at either of the tested time points. The physical stability of the agitation samples was evaluated by SE-HPLC. The results demonstrated that although the observed changes were small, it appears that the formulations containing Poloxamer 188 may be destabilizing upon agitation.

The sub-visible particle counts were evaluated for select agitation samples. The particle counts and size range were all lower than the required specification of USP 788.

Similar measurements were performed for the freeze/thaw samples. These results showed that no significant change in GM37v2 concentration was observed after multiple freeze-thaw cycles.

Upon evaluation of the SE-HPLC data, although the changes are small, it does appear that F04 (study 2C) and F05 (study 2C) (Histidine buffer formulations containing Poloxamer 188) demonstrates the greatest increase after multiple freeze-thaw cycles.

Also for the freeze/thaw samples the particle counts and size range were all lower than the required specification of USP 788.

Conclusion/summary of surfactant study

Study 1C:

Overall, based on the results of all analytical methods utilized in this study (visible particles, reduced and non-reduced CE SDS, GP-HPLC and sub-visible particles) it was concluded that the inclusion of 0.02 % (w/v) Polysorbate 80 in the formulation reduced the overall number of sub-visible particles and hence adding polysorbate 80 to the candidate formulation produced an optimal clinically suitable formulation.

Study 2C:

The tested formulation candidates indicate that in these formulations GM37v2 does not appear to exhibit significant changes in physical stability upon exposure to agitation or freeze-thaw stress. However, it does appear that, in general, a surfactant is beneficial for the performance of the formulations in terms of the physical stability. Further, Polysorbate 80 (polysorbate 80) appears to be slightly preferred over Poloxamer 188, which appears to be slightly destabilizing compared to polysorbate 80. Accordingly, adding polysorbate 80 to the formulation candidate would likely be beneficial for maintaining interfacial stability, with a target concentration likely to be near 0.02% (w/v).

Example D – Long term storage stability

Two formulations were evaluated for their performance in regard to long-term storage stability. This study collected stability data over the course of six months at 5° and 25° C.

Table 33: Formulations investigated in Example D

Verification Formulations	Composition
Lead	25 mM Histidine, 100 mM Sucrose, 100 mM Sodium Chloride, 0.02% Polysorbate 80, pH 6.0, 200 mg/mL GM37v2
Backup	40 mM Histidine, 100 mM Sodium chloride, 0.02% Polysorbate 80, pH 6.0, 200 mg/mL GM37v2

Summarized results of Example D:

Both the lead and backup formulations displayed good stability upon storage at 5°C up to six months and 25° C up to three months. However, in terms of sub-visible particles formation and chemical stability by CEX-HPLC, the lead formulation (25 mM Histidine, 100 mM sucrose, 100 mM sodium chloride, 0.02% polysorbate 80, pH 6.0, 200 mg/mL GM37v2) performed better than the backup formulation (40 mM Histidine, 100 mM sodium chloride, 0.02% polysorbate 80, pH 6.0, 200 mg/mL GM37v2) as predominantly differentiated by the observed trends under accelerated conditions of 25° C. Both were comparable in terms of stability measured by SE-HPLC, where both exhibited losses that extrapolate to < 2% over the course of two years. Neither formulation showed any appreciable loss of protein over the course of the study and the pH remained constant for all of the stored samples.

A specific liquid pharmaceutical composition containing 25 mM histidine/histidine hydrochloride, 100 mM sucrose, 100 mM sodium chloride, 0.02% Polysorbate 80, pH 6.0 with a concentration of 53.0 ± 5 mg/mL GM37v2 and a nominal volume of 20 mL was also tested for stability. These tests showed that this composition is suitable for long term storage at suitable conditions such as 5°C ± 3°C and maintains the physical and chemical integrity of the antibody GM37v2 for at least 36 months.

Further the specific liquid pharmaceutical composition containing 25 mM histidine/histidine hydrochloride, 100 mM sucrose, 100 mM sodium chloride, 0.02% Polysorbate 80, pH 6.0 with a concentration of 53.0 ± 5 mg/mL GM37v2 was investigated by accelerated stress condition at 25°C which showed that this formulation was stable for at least 6 months under such conditions.

Consolidated conclusions from Examples A-C and D:

From study 1A, 1B and 1C it was found that a formulation comprising GM37v2, 25 mM L-histidine, 100 mM NaCl, 100 mM sucrose and 0.02 % Polysorbate 80 at pH 6.0 is the most suitable formulation to progress into clinical development.

Study 2A, 2B and 2C revealed that the optimal pH is likely to be near 6.0, using a Histidine buffer concentration of 20-40 mM. The nature of the tonicity modifier does not appear to be critical, but NaCl is preferred, due to the observed viscosity reducing effect. Polysorbate 80 is beneficial for maintaining interfacial stability, with a target concentration near 0.02% (w/v). Therefore, formulations comprising 30-225 mg/mL GM37v2, 20-40 mM Histidine, 100 mM NaCl, 100 mM sucrose and 0.02 % Polysorbate 80 at pH 6.0 are the optimal formulation candidate.

Example D revealed by using accelerated stress condition at 25°C for three to six months that the formulations comprising 25 mM Histidine, 100 mM sucrose, 100 mM sodium chloride, 0.02% polysorbate 80, at pH 6.0, and 53 or 200 mg/mL GM37v2, are stable upon longer-term storage. This also applies for a relatively high GM37v2 concentration of 200 mg/mL and even at this elevated concentration, the above formulation exhibits a low viscosity of < 10 cP. Accordingly, the work presented above identified formulation candidates which are suited for clinical use, this especially applies to the ones comprising histidine buffer at about pH 6.0 and even more specifically to the compositions further comprising NaCl, sucrose and Polysorbate 80 as they exhibit desired properties in the field of pharmaceutical compositions, such as high stability and low viscosity, over a large range of GM37v2 concentrations (30-225 mg/mL). Accordingly, the identified formulation candidates are very flexible and useful in clinical settings to administer various dosing regimens of GM37v2 to patients.

CLAIMS

1. A method of treating early multiple system atrophy (MSA) or MSA-C, wherein said method comprises administering an effective amount of a monoclonal anti-alpha synuclein antibody to a human subject in need thereof, wherein said monoclonal anti-alpha synuclein antibody binds an epitope within amino acids 112-117 (SEQ ID NO:9 (ILEDMP)) of human alpha synuclein (SEQ ID NO:10), and wherein said monoclonal antibody 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**;
    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**.

2. The method of treating MSA according claim 1, wherein the human subject has an UMSARS total score below 40 at treatment initiation.

3. The method of treating MSA according to any of claims 1-2, wherein the human subject has early MSA-C.

4. The method of treating MSA according to any one of claims 1-3, wherein the human subject has MSA-C and an UMSARS total score below 40 at treatment initiation.

5. The method of treating MSA according to any one of claims 1-4, wherein said monoclonal antibody comprises a heavy chain variable domain having the amino acid sequence of **SEQ ID NO:31** and a light chain variable domain having the amino acid sequence of **SEQ ID NO:8**.

6. The method of treating MSA according to any one of claims 1-5, wherein said monoclonal antibody is a human IgG1 antibody.

7. The method of treating MSA according to any one of claims 1-6, wherein said monoclonal antibody comprises a constant heavy chain domain having the amino acid sequence of **SEQ ID NO:18** and a kappa light chain constant domain having the amino acid sequence of **SEQ ID NO:17**.

8. The method of treating MSA according to any one of claims 1-7, wherein said monoclonal antibody is Amlenetug.

9. The method of treating MSA according to any one of claims 1-8, wherein said monoclonal antibody is administered intravenously about every 4 weeks.

10. The method of treating MSA according to any one of claims 1-8, wherein said monoclonal antibody is administered intravenously about once monthly.

11. The method of treating MSA according to any one of claims 1-10, wherein said monoclonal antibody is administered intravenously at a dose of about 2100 mg.

12. The method of treating MSA according to any one of claims 1-10, wherein said monoclonal antibody is administered intravenously at a dose of about 4200 mg.

13. The method of treating MSA according to any one of claims 1-12, wherein the treatment consists of slowing clinical progression by at least 5%, such as at least 10%, such as at least 15%, such as at least 20%, such as at least 25%, such as at least 30%, such as at least 35%, such as at least 40%, such as at least 45%, such as at least 50%, such as at least 55%, such as at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%, such as at least 85% or such as at least 90%.

14. The method of treating MSA according to any one of claims 1-13, wherein the treatment effect is quantified by longitudinal changes from baseline score using the Unified Multiple System Atrophy Rating Scale total score (UMSARS TS) or using the modified UMSARS (mUMSARS).

15. The method of treating MSA according to any one of claims 1-14, wherein the treatment effect is quantified by longitudinal changes from baseline in Brain Volume, as measured by Volumetric MRI (vMRI).