TREATMENT OF TAUOPATHIES WITH TAU-BINDING ANTIBODIES

FIELD OF THE INVENTION

The present invention relates to the treatment of tauopathies, in particular the treatment of tauopathies such as Progressive Supranuclear Palsy (PSP) and/or Alzheimer's Disease (AD) with a tau-binding antibody or antigen-binding fragment thereof.

BACKGROUND OF THE INVENTION

Pathologically, tau has been shown to contribute to the development of the group of neurodegenerative diseases which are classed as tauopathies. Tauopathies occur as a result of misfolding and aggregation of the tau protein, which then affects normal neuronal function (Zhang et al., Mol Neuro, 2022). Tau is coded for by the microtubule-associated protein tau gene (MAPT), that is widely distributed in neurons and also expressed in glial cells. In its nonpathological state, tau is a highly soluble protein, which occurs in the central nervous system in 6 main isoforms due to alternative MAPT gene splicing, ranging from 352 to 441 amino acids in length. These isoforms can have 0, 1, or 2 N-terminal inserts (0N, 1N, or 2N), and either 3 or 4 C-terminal "repeat" sequences (3R or 4R). These 30 to 32 amino acid C-terminal repeat sequences, R1, R2, R3, and R4, together constitute the tau MTBR (microtubule binding region).

In physiological conditions, tau exists in equal balance between 3R and 4R isoforms (Irwin, Parkinsonism Relat Disord. 2016;22 Suppl 1: S29-33), is mainly concentrated in the distal part of axons, and is natively unfolded (Huang et al, Cell Mol Life Sci. 2016;73(1):1-21). Depending on the relative abundance of different tau isoforms in the pathological inclusions found in brain specimens of patients, tauopathies are usually classified as 3R tauopathies (i.e., Pick's disease), 3R/4R tauopathies (i.e., Alzheimer's disease (AD)), and 4R tauopathies (i.e., progressive supranuclear palsy (PS), corticobasal degeneration (CBD), argyrophilic grain disease, and globular glial tauopathies) (Irwin, Parkinsonism Relat Disord. 2016;22 Suppl 1: S29-33).

PSP is a rare and fatal tauopathy, whose pathology begins with the accumulation of tau in the subcortical and brain stem nuclei, as well as regions related to symptoms such as sleeping disorders, motor dysfunction and Parkinsonism (Coughlin et al., Parkinsonism Relat Disord 2020 Apr;73:105-116). The progression of PSP results in the reduction of quality of life (QoL) and autonomy of people living with the disease, as they experience worsening dysarthria, cognitive

difficulties, and physical disability (Agarwal and Gilbert, StatPearls Publishing 2023), which in turn affects the quality of life of their caregivers and families. Currently, PSP is thought to have a global prevalence of approximately 5-6 per 100 000 (CurePSP Handbook, 2020), with an average time from onset of symptoms to death of 7 years (Hoglinger et al., Mov Dis, 2017; 32: 853–64; Agarwal and Gilbert, StatPearls Publishing 2023). There are currently no approved disease-modifying treatments to slow down the progression of tauopathies such as PSP or CBD, nor their underlying causes; current treatments only serve to reduce the symptoms of people living with these conditions (Cummings et al., Alzheimer's Dement. 2023; 9: e12385; Yiannopoulou et al., Biomedicines, 2019 Dec 9;7(4):97). The relentless progression of PSP, short time from symptom onset to death, as well as challenges with accurate and timely diagnosis therefore highlight the high unmet need for disease-modifying treatments.

In Alzheimer's disease, the hyperphosphorylation of tau contributes to the amyloid cascade which is responsible for the development of the disease (Yiannopoulou et al., Biomedicines, 2019 Dec 9;7(4):97). In the case of AD aducanumab and lecanemab, two beta-amyloid targeting antibodies, have been approved by the FDA after having demonstrated a slowing of disease progression in clinical trials. Alzheimer's disease (AD) pathology is characterised by formation of both neuronal tau fibrils and extracellular amyloid plaques. The behavioral symptoms of AD correlate with the accumulation of plaques and tangles, and they are a direct consequence of the damage and destruction of synapses that mediate memory and cognition. These treatments will nonetheless address only one of the two agents that are believed to be directly related to the pathology.

WO 2017/005734 describes tau-binding antibodies with a specificity to the central region of human tau. In a tau seeding experiment, these antibodies blocked the seeding of both human AD and PSP tau. Based on these results, targeting the central region of tau blocked the seeding of human tau, whereas targeting the N-terminal region did not.

Emerging data on the biology of human tau suggests that the efficacy of passive antibody treatment is likely to be influenced by the fragmentation pattern of the tau molecule and the antibody epitope (Hoglinger et al. Lancet Neurology 2021). Previous studies have investigated antibodies that targeted the N-terminal region of human tau. Examples of those studies were two Phase 2 clinical trials, which assessed the safety and efficacy of gosuranemab (NCT03068468, N=486) and tilavonemab (NCT02985879, N=377) in people with PSP. These antibodies however,

failed to demonstrate clinical efficacy. Similarly, the antibodies also failed in Phase 2 clinical trials in people with Alzheimer's disease.

Thus, the need for effective antibody treatments to target human tau and hence tauopathies such as Alzheimer's disease and PSP remains.

SUMMARY OF THE INVENTION

The invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or antigen-binding fragment thereof, wherein the tau-binding antibody or antigen-binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

The invention further provides a fixed dosing approach based on which of two weight ranges a subject falls in. Hence, the present invention further provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering a fixed dose of the tau-binding antibody or antigen-binding fragment to the subject, wherein:

(a) the subject has a body weight of 40 kg up to, but not including, 60 kg and the fixed dose is 4.5g to 5.5g of the tau-binding antibody or antigen-binding fragment; or

(b) the subject has a body weight of 60 kg to 100 kg and the fixed dose is 6.5g to 7.5g of the tau-binding antibody or antigen-binding fragment,

wherein the tau-binding antibody or antigen-binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. UP0047 - Dose proportionality of bepranemab exposure in serum (PK-PPS). (A) Cmax; (B) AUC. AUC=area under the concentration-time curve from time 0 to infinity; AUC(0-t) = area under the concentration-time curve from time 0 to time t; CI = confidence interval; Cmax = maximum observed concentration; PK-PPS = Pharmacokinetic-Per Protocol Set. Note: Regression line formula for AUC (original values – linear scale) was y=11874.95*x+21800.79. Note: Regression line formula for AUC(0-t) (original values – linear scale) was y=11433.58*x+22368.11. Note: Regression line formula for Cmax (original values – linear scale) was y = 26.376*x-21.074.

Figure 2. UP0065 - Dose proportionality of bepranemab exposure in serum (PK-PPS). (A) Cmax; (B) AUC. AUC = area under the concentration-time curve from time 0 to infinity; AUC(0-t) = area under the concentration-time curve from time 0 to time t; CI=confidence interval; Cmax = maximum observed concentration; PK PPS=Pharmacokinetic-Per Protocol Set.
The slight deviation from dose proportionality in the exposure (AUC) is due to the variability between participants, as this analysis was based on a limited sample size (6 subjects per arm).

Figure 3. Schedule of activities and endpoint recording for PSP003.

Figure 4. Overview of incidence of TEAEs in PSP003.

Figure 5. Most frequent TEAEs by SOC and PT.

Figure 6. Free tau species targeted by bepranemab levels in CSF - % change from baseline to week 1: all participants. Due to technical & biological considerations, study sample data were reported as a percentage of baseline data, and not as concentration data (neat sample analysis only). Data should be viewed as qualitative rather than quantitative. In the graph the left--hand column shows the results for placebo and the right-hand column the results for bepranemab.

Figure 7. CSF free tau inhibition in placebo versus 90 mg/kg bepranemab groups CSF=cerebrospinal fluid. In the main graph, the five highest plot points (black) are those for placebo, with the rest for those given 90mg/kg bepranemab.

Figure 8. Individual values of CSF free tau over time, showing the decrease of free tau in CSF over time in 90mg/kg treated groups versus placebo.

Figure 9. Predicted bepranemab steady state average (Cavg) and maximal (Cmax) concentrations over a 40-100 kg body weight range, showing comparability in both parameters for fixed doses of 4.8 g (for 40-<60 kg) and 7.2 g (for ≥60-100 kg) [red curve – in

each graph the red curve is the one that starts second highest at the Y axis] versus a weight-adjusted dose of 90 mg/kg [blue curve - in each graph the blue curve is the one that lowest at the Y axis].

DETAILED DESCRIPTION OF THE INVENTION

This invention pertains to methods of treating a tauopathy in which the administration of a tau-binding antibody is beneficial. The present invention pertains to particularly effective doses and dosing regimens for treating tauopathies. The present invention provides the methods themselves. The present invention also provides tau binding antibodies and antigen-binding fragments thereof for use in such methods. It also provides use of tau binding antibodies and antigen-binding fragments thereof for the manufacture of a medicament for treating tauopathies. Although, the present invention is applicable to tauopathies in general, particular tauopathies of interest are Progressive Supranuclear Palsy (PSP) and Alzheimer's Disease (AD).

Tau binding antibodies and antigen-binding fragments thereof

The present application is based in part on the identification of particularly effective dose and dosing schedules for tau-binding antibodies or binding fragments thereof in the treatment of tauopathies. The present section sets out examples of particular tau-binding antibodies and antigen-binding fragments thereof that may be used in the present invention. As is customary in the field, Tau residue numbering in this text refers to Tau isoform 2 of SEQ ID No.: 11 (NCBI reference sequence: NP_005901.2).

In one embodiment, the tau binding antibody or antigen-binding fragment thereof binds to the central region of the human tau protein. Optionally the antibody or antigen-binding fragment thereof employed in the invention recognizes an epitope comprising at least the amino acids residues of S238, A239, S241, T245, A246 of SEQ ID No.: 11. This region is just before the first MTBR repeat region present in all 6 isoforms of Tau that may be found in the central nervous system. In a further particular embodiment, the tau-binding antibody or binding fragment thereof binds to an epitope comprising the amino acid residues of S238, A239, S241, T245, A246, and one or more residues selected from S235, S237, K240, R242, L243, Q244, V248, and M250 of SEQ ID No.: 11. In a further particular embodiment, the epitope bound by the tau-binding

antibody or binding fragment thereof is determined by heteronuclear single quantum coherence nuclear magnetic resonance (HSQC NMR).

In one embodiment, the antibody or antigen-binding fragment thereof is a monoclonal antibody or antigen-binding fragment thereof. In one particular embodiment the antibody or antigen-binding fragment thereof is a humanized monoclonal Tau-binding antibody or antigen-binding fragment thereof.

In another embodiment, the tau-binding antibody or binding fragment thereof binds to both soluble human and paired helical filaments (PHF) of human tau.

Examples of antibodies and antigen-binding fragments thereof which may be employed in the present invention are described in WO 2017/005734. WO 2017/005734 is incorporated by reference in its entirety. It is also incorporated by reference in relation to the tau binding antibodies and antigen-binding fragments thereof described.

Table 1 below sets out particular antibody sequences to be employed in the present invention as well as providing the amino acid sequence of human tau protein.

Table 1

CDR-L1 SEQ ID NO 1	RSSQSLEYSDGYTYLE
CDR-L2 SEQ ID NO 2	EVSNRFS
CDR-L3 SEQ ID NO 3	FQATHNPYT
CDR-H1 SEQ ID NO 4	GFSLTSNDIA
CDR-H2 SEQ ID NO 5	TIWTDGSTNYNTAVQS
CDR-H3 SEQ ID NO 6	HRLYYGAFDY
VL SEQ ID NO 7	DIVMTQTPLSLSVTPGQPASISCRSSQSLEYSDGYTYLEWYLQKPGQSPQL LIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQATHNPYT FGQGTKLEIK

VH SEQ ID NO 8	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSNDIAWIRQPPGKGLEWMGTI WTDGSTNYNTAVQSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARHRLYY GAFDYWGQGTMVTVSS
LC SEQ ID NO 9	DIVMTQTPLSLSVTPGQPASISCRSSQSLEYSDGYTYLEWYLQKPGQSPQL LIYEVSNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQATHNPYT FGQGTKLEIK*RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW* *KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ* *GLSSPVTKSFNRGEC*
HC SEQ ID NO 10	EVQLQESGPGLVKPSETLSLTCTVSGFSLTSNDIAWIRQPPGKGLEWMGTI WTDGSTNYNTAVQSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARHRLYY GAFDYWGQGTMVTVSS*ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPE* *PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVD* *HKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP* *EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV* *LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMT* *KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL* *TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK*
Tau protein SEQ ID NO 11	MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTP TEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTT AEEAGIGDTPSLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIAT PRGAAPPGQKGQANATRIPAKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPG TPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKN VKSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSV QIVYKPVDLSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSL DNITHVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVSGDTSPRHL SNVSSTGSIDMVDSPQLATLADEVSASLAKQGL

In one particular embodiment, the tau-binding antibody or binding fragment thereof comprises a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable

region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

In a further embodiment, the tau-binding antibody or binding fragment thereof comprises a light chain variable region comprising SEQ ID No.: 7, and a heavy chain variable region comprising SEQ ID No.: 8.

In another embodiment of the present invention, the tau-binding antibody or binding fragment thereof comprises a light chain comprising SEQ ID No.: 9, and a heavy chain comprising SEQ ID No.: 10. In a further optional embodiment, the antibody comprises two such heavy chains and two such light chains.

An antibody or antigen-binding fragment of the present invention may be provided in any suitable format. In one particular embodiment, an antibody or antigen-binding fragment thereof of the present invention may be an IgG class antibody or fragment thereof. In one embodiment, it may be an IgG1, IgG2, IgG3, or IgG4 isotype antibody and in particular IgG1. In another embodiment, an antibody of antigen-binding fragment thereof of the invention may be an IgA, IgE, IgD, or IgM class antibody. In a particular alternative embodiment, the antibody is a monoclonal IgG4 antibody.

In another alternative embodiment, the antibody employed is bepranemab. Hence, for any of the embodiments set out herein bepranemab may be employed. Bioequivalents of bepranemab may also be employed. Antibodies or antigen-binding fragments thereof that are able to cross-block any of the antibodies set out herein may be employed. In one embodiment, an antibody that is able to cross-block bepranemab is employed. In one embodiment, an antibody that is able to bind to substantially the same epitope of bepranemab is employed. It should be noted that another name for bepranemab is UCB0107, and therefore these terms may be used interchangeably.

The present disclosure refers to antibodies and antibody fragments. Wherever mention is made of an antibody an antibody fragment which is an antigen-binding fragment may be employed unless specifically stated otherwise. Hence, antibodies of the present invention may comprise a complete antibody having full length heavy and light chains or be an antigen-binding fragment, for instance, a Fab, modified Fab, Fab', modified Fab', F(ab')2, Fv, single domain antibody (e.g. VH or VL or VHH), scFv, bi, tri or tetra-valent antibody, Bis-scFv, diabody, triabody, tetrabody or epitope-binding fragments of any of the above (see for example Holliger and Hudson, 2005, Nature Biotech. 23(9):1126-1136; Adair and Lawson, 2005, Drug Design Reviews - Online 2(3),

209-217). The methods for creating and manufacturing antibody fragments are well known in the art (see for example Verma et al., 1998, Journal of Immunological Methods, 216, 165-181). Other antibody fragments for use in the present invention include the Fab and Fab' fragments described in International patent applications WO2005/003169, WO2005/003170 and WO2005/003171. Multi-valent antibodies may comprise multiple specificities, e.g. bispecific or may be monospecific (see for example WO 92/22853, WO05/113605, WO2009/040562 and WO2010/035012). Examples of possible antibody formats are known in the art, for example as disclosed in the review "The coming of Age of Engineered Multivalent Antibodies", Nunez-Prado et al Drug Discovery Today Vol 20 Number 5 Mar 2015, page 588-594, D. Holmes, Nature Rev Drug Disc Nov 2011:10; 798, Chan and Carter, Nature Reviews Immunology vol. 10, May 2010, 301 incorporated herein by reference.

Doses

In one embodiment, the present invention is based on the identification of particularly effective dose of tau-binding antibody or antigen-binding fragment thereof for treating a tauopathy. The doses are particularly effective for tau-binding antibodies or antigen-binding fragments thereof that bind the central region of tau protein, such as any of the antibodies and antigen-binding-fragments thereof disclosed in WO 2017/005732. In one embodiment a dose is 30 mg/kg to 120 mg/kg of antibody or antigen-binding fragment thereof.

In one embodiment, the dose is 30 mg/kg, 45 mg/kg, 60 mg/kg, 90 mg/kg or 120 mg/kg of antibody or antigen-binding fragment thereof. In one embodiment a dose is 45 mg/kg to 90 mg/kg. In a particular alternative embodiment of the invention a dose or doses of about 45 mg/kg or about 90 mg/kg of the tau-binding antibody or antigen-binding fragment thereof are employed. In an alternative embodiment of the invention a dose or doses of 45 mg/kg or 90 mg/kg of the tau-binding or antigen-binding fragment thereof are employed.

In one embodiment, it is 40 mg/kg to 50 mg/kg. In another alternative embodiment, the dose is about 45 mg/kg. Such doses may be administered to a patient with a tauopathy, such as any of those set out herein. In one embodiment, such doses are administered to a sufferer with AD. In another they are administered to a sufferer with PSP.

In another alternative embodiment, the dose is 85 mg/kg to 95 mg/kg. In another alternative embodiment, the dose is about 90 mg/kg. Such doses may be administered to a patient with a

tauopathy, such as any of those set out herein. In one embodiment, such doses are administered to a sufferer with AD. In another they are administered to a sufferer with PSP.

Fixed dosing

In one embodiment, a fixed dose is given, rather than one based on mg/kg. In one embodiment, the fixed dose is from 3g to 10g. In one embodiment the fixed dose is from 3g to 8g. In one embodiment, the fixed dose is from 4g to 8g. In one embodiment a fixed dose is from 3g to 6g. In one embodiment it is from 3g to 5g. In another embodiment a fixed dose is from 5g to 9g. In one embodiment, it is from 6g to 8g.

In one embodiment, a fixed dose of antibody or antigen-binding fragment thereof is administered, rather than based on a dosage calculated based on mg/kg and the exact bodyweight of the subject. In one embodiment, the dose given is based on what body weight range the subject falls in.

In one embodiment, the subject has a body weight of 40 kg up to, but not including, 60kg and is given a fixed dose of 4.0g to 6.0g. In one embodiment, the fixed dose for that weight range is 4.5g to 5.5g. In a further embodiment, the fixed dose for that weight range is 4.6g to 5.0g. In a further embodiment, the fixed dose for that weight range is 4.7g to 4.9g.

In one embodiment, the subject has a body weight of 40kg up to, but not including, 60kg and is given a fixed dose of 4.8g.

In one embodiment, the subject has a body weight of 60kg up to 100kg and is given a fixed dose of 6.0g to 8.0g. In one embodiment, the fixed dose for that weight rage is 6.5g to 7.5g. In one embodiment, the fixed dose for that weight rage is 6.8g to 7.4g. In a further embodiment, the fixed dose for that weight range is 7.0g to 7.4g. In a further embodiment, the fixed dose for that weight range is 7.1g to 7.3g.

In one embodiment, the subject has a body weight of 60kg up to100kg and is given a fixed dose of 7.5g.

Number and timing of doses

In one embodiment, a plurality of doses will be administered, for example at least 4 doses. In one alternative embodiment, at least 12 doses are administered. In a further embodiment, at least

20 doses are administered. In one embodiment from 4 to 30 doses are administered. In one embodiment, dosing is continued indefinitely.

As with treatment of any disease, clinical judgement must be exercised when considering the length of treatment. However given that tauopathies are neurodegenerative diseases of relatively slow progression, and the method of treating them according to the current invention is preferably able to slow progression of the symptoms, it is considered that a method according to the current invention will include administering the tau-binding antibody or binding fragment thereof to the human subject in need thereof for, at least 12 weeks, at least 24 weeks, at least 52 weeks, at least 68 weeks or at least 80 weeks, or until no longer clinically relevant. Given the nature of these diseases there is a potential requirement for life-time administration.

As typically more than one dose of antibody or antigen-binding fragment thereof is administered there will be an interval between each pair of doses. A skilled person would understand that dosing intervals in the clinical setting are expressed as a function of time, and these timing intervals may be typically expressed in days, weeks or months. In one particular embodiment, doses are administered at regular intervals, so that the intervals are the same or approximately the same each time. In one embodiment, doses are administered at intervals of 3 to 5 weeks. In another embodiment, doses are administered about monthly. In another optional embodiment, doses may be administered about every 4 weeks. In a further particular embodiment, the tau-binding antibody is administered once every 4 +/- 1 weeks, or alternatively once every 21 to 35 days.

Routes of administration

The tau-binding antibody or antigen-binding fragment thereof may be administered by any suitable route to the patient. Examples of optional routes include intravenous, subcutaneous or intramuscular administration of the tau-binding antibody or antibody fragment to the individual in need thereof.

In another embodiment, the route of administration is intravenous. In one particular embodiment, the administration is via intravenous injection. In one embodiment, the administration is via intravenous infusion.

In one embodiment, the administration is subcutaneous. Subcutaneous administration is advantageous because the patient may self-administer a therapeutic substance, e.g., a tau-binding

antibody or antibody fragment thereof, which is convenient for both the patient and the health care provider.

Illustrative optional regimens

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or binding fragment thereof. In one particular embodiment, the tauopathy is AD. In another particular embodiment it is PSP.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In another particular embodiment it is PSP.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject a plurality of doses of 30 mg/kg to 120 mg/kg of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In one particular embodiment, it is PSP.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject a plurality of doses of 40 mg/kg to 50 mg/kg of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one particular embodiment, the doses are 4 weeks apart. In a preferred embodiment, the dose is about 45 mg/kg. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In one particular embodiment, it is PSP.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject a plurality of doses of 85 mg/kg to 95 mg/kg of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one embodiment, they are 4 weeks apart. In a particular embodiment, the dose is about 90 mg/kg. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In one particular embodiment, it is PSP.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating PSP in a human subject in need thereof, the method comprising administering to the human subject a plurality of doses of 85 mg/kg to 95 mg/kg of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In a particular embodiment, the dose is about 90 mg/kg. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2,

and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating AD in a human subject in need thereof, the method comprising administering to the human subject a plurality of doses of 40 mg/kg to 50 mg/kg of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In a particular embodiment, the dose is about 45 mg/kg. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one embodiment, at least 10 doses are administered. In another embodiment, at least 20 doses are administered.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating AD in a human subject in need thereof, the method comprising administering to the human subject a plurality of doses of 85 mg/kg to 95 mg/kg of the tau-binding antibody or antigen-binding fragment thereof, wherein the doses are administered 3 to 5 weeks apart. In a particular embodiment, the dose is about 90 mg/kg. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one embodiment, at least 10 doses are administered. In another embodiment, at least 20 doses are administered.

In an optional embodiment, in any of the embodiments set out above, the administration is intravenous. In one more particular embodiment, it is via intravenous infusion. In another, it is via subcutaneous injection.

In one optional embodiment, in any of the embodiments set out above the doses are administered about once a month or once every 4 weeks.

Illustrative fixed dose regimens for subjects with body weight 40kg up to, but not including 60 kg

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject having a body weight of 40kg up to, but not including 60 kg at least one dose of 4.0g to 5.5g of the tau-binding antibody or binding fragment thereof. In one particular embodiment, the tauopathy is AD. In another particular embodiment it is PSP. In one embodiment the dose is 4.5g to 5.0g. In one embodiment, the dose is 4.8g.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof having a body weight of 40kg up to, but not including 60 kg, the method comprising administering to the human subject at least one dose of 4.5g to 5.5g of the tau-binding antibody or binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In another particular embodiment it is PSP. In one embodiment the dose is 4.5g to 5.0g. In one embodiment, the dose is 4.8g.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof having a body weight of 40kg up to, but not including 60 kg, the method comprising administering to the human subject a plurality of doses of 4.5g to 5.5g of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular

embodiment, the tauopathy is AD. In one particular embodiment, it is PSP. In one embodiment the dose is 4.5g to 5.0g. In one embodiment, the dose is 4.8g.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject having a body weight of 40kg up to, but not including 60 kg a plurality of doses of 4.5g to 5.0g of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one particular embodiment, the doses are 4 weeks apart. In a preferred embodiment, the dose is about 4.6g to 4.9 g. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In one particular embodiment, it is PSP. In one embodiment, the dose is 4.8g.

In an optional embodiment, in any of the embodiments set out above, the administration is intravenous. In one more particular embodiment, it is via intravenous infusion. In another, it is via subcutaneous injection.

In one optional embodiment, in any of the embodiments set out above the doses are administered about once a month or once every 4 weeks.

Illustrative fixed dose regimens for subjects with body weight 60kg up to 100 kg

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject having a body weight of 60kg up to 100 kg at least one dose of 6.5g to 7.5g of the tau-binding antibody or binding fragment thereof. In one particular embodiment, the tauopathy is AD. In another particular embodiment it is PSP. In one embodiment the dose is 7.0 to 7.5g. In one embodiment, the dose is 7.2g.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof having a body weight of 60kg up to 100 kg, the method comprising administering to the

human subject at least one dose of 6.5g to 7.5g of the tau-binding antibody or binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In another particular embodiment it is PSP. In one embodiment the dose is 7.0 to 7.5g. In one embodiment, the dose is 7.2g.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof having a body weight of 60kg up to 100kg, the method comprising administering to the human subject a plurality of doses of 6.5g to 7.5g of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In one particular embodiment, it is PSP. In another particular embodiment it is PSP. In one embodiment the dose is 7.0 to 7.5g. In one embodiment, the dose is 7.2g.

In one embodiment, the present invention provides a tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject having a body weight of 60kg up to 100 kg a plurality of doses of 6.5g to 7.5g of the tau-binding antibody or binding fragment thereof, wherein the doses are administered 3 weeks to 5 weeks apart. In one particular embodiment, the doses are 4 weeks apart. In a preferred embodiment, the dose is about 45 mg/kg. In one particular embodiment, the antibody or antigen-binding fragment thereof comprises: a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a

CDR3 selected from SEQ ID No.: 6. In one alternative embodiment, the antibody is bepranemab. In one particular embodiment, the tauopathy is AD. In one particular embodiment, it is PSP. In another particular embodiment it is PSP. In one embodiment the dose is 7.0 to 7.5g. In one embodiment, the dose is 7.2g.

In an optional embodiment, in any of the embodiments set out above, the administration is intravenous. In one more particular embodiment, it is via intravenous infusion. In another, it is via subcutaneous injection.

In one optional embodiment, in any of the embodiments set out above the doses are administered about once a month or once every 4 weeks.

In one embodiment where a subject alters body weight they will be moved to the appropriate fixed dose for the weight range they fall in, so either that for 40kg up to, but not including 60kg, or that for 60kg up to 100kg.

Methods of treatment and manufacture of medicaments

The present disclosure sets out a tau-binding antibody or antigen-binding fragment thereof for use in various methods of treatment. The present invention also provides the methods themselves. It also provides for the use of a tau-binding antibody or antigen-binding fragment thereof in the manufacture of a medicament for treating a tauopathy as set out. Hence, where a tau-binding antibody or antigen-binding fragment thereof for use, a method of treatment, or use in the manufacture of a medicament is set out, the equivalent other format is also provided.

Pharmaceutical compositions and formulation

The tau-binding antibody or antibody fragment of the invention can be incorporated into pharmaceutical composition. Thus, where reference herein is made to an antibody or antigen-binding fragment thereof a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof may be provided or employed. Typically, the pharmaceutical composition comprises the tau-binding antibody or antibody fragment of the invention and/or a pharmaceutically acceptable carrier and/or other active ingredient such as galantamine, rivastigmine, or donepezil.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying

agents, and the like that are physiologically compatible and are suitable for administration to a subject for the methods described herein. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion. The compositions of this invention may be in a variety of forms. These include, for example, liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, powders and liposomes. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies.

In one embodiment, the formulation is specific for one of the administration routes set out herein, for instance compositions suitable for administration to a subject intravenously, subcutaneously or intramuscularly may be provided. Hence, in another embodiment of the invention is a pharmaceutical composition comprising the tau-binding antibody or antigen-binding fragment according to any of the embodiments of the invention and a pharmaceutically acceptable carrier wherein the composition is prepared for intravenous, subcutaneous or intramuscular administration to the individual in need thereof.

In another embodiment the composition is part of a kit with instructions for use, including instructions and optionally a device for intravenous, subcutaneous or intramuscular administration to the individual in need thereof. In one embodiment, the instructions set out a dosage and/or regimen as disclosed herein.

Tauopathies and patient assessment

The present invention may be used to treat tauopathies in general. Examples of particular tauopathies to be treated are Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration and Alzheimer's disease (AD). In an alternative embodiment the tauopathy is PSP or AD.

Progressive supranuclear palsy (PSP) is characterised by the misfolding and aggregation of pathological tau which spreads through the brain, causing neurodegeneration and resultant brain

atrophy (Colin et al Acta Neuropathol 2020; 139: 3–25; Gong et al. Curr Med Chem 2008; 15: 2321–8; Orr et al Trends Pharmacol Sci 2017; 38: 637–48). Pathology in PSP begins with tau accumulation in subcortical and brainstem nuclei, the globus pallidus and striatum, regions associated with symptoms such as postural instability, sleep disorders, ocular motor dysfunction, and Parkinsonism. This is followed by tau accumulation in cortical areas including the frontal, parietal, and temporal lobes, which are associated with symptoms such as cognitive impairment and behavioural alterations, apraxia, and impaired language function, respectively (Coughlin et al. Parkinsonism Relat Disord 2020; 73: 105–16). There are a number of clinical phenotypes of PSP, characterised by different combinations of these symptoms: Richardson syndrome (PSP RS), PSP predominant parkinsonism (PSP P) and PSP progressive gait freezing (PSP PGF), among others (Hoglinger et al Mov Disord 2017; 32: 853–64). In one particular embodiment of the invention, the tauopathy is selected from PSP RS, PSP P and PSP PGF.

Initial symptoms of PSP RS typically develop in patients aged approximately 65 years and include gait difficulties and falls. As the disease progresses, patients may experience worsening parkinsonism, dysarthria, dysphagia, frontal cognitive difficulties, and supranuclear ophthalmoplegia. Disease progression is rapid and relentless, with increased physical disability; on average, PSP RS advances from symptom onset to death in 7 years, with a dependency on care developing within 3–4 years from presentation (Williams et al Brain 2005; 128: 1247–58; Hoglinger et al Mov Disord 2017; 32: 853–64). The average age at death in people with PSP-RS is earlier at 72.1 years, compared with 75.5 years in people with PSP P.

There are currently no approved treatments to target the underlying cause of PSP, or to slow down disease progression.

In one alternative embodiment, a treatment of the invention results in a slowing of disease progression as measured by adequate rating tools recommended by the regulatory agencies. One such currently available tool is the PSP Rating Scale. The PSP Rating Scale (PSPRS) is a prospectively validated physician-rated measure of disease severity for PSP, measured by 28 items within 6 categories: daily activities, mentation, bulbar, ocular motor, limb motor, and gait/midline exam. The rater assigns 0–2 or 0–4 points for each item, yielding a total PSPRS score from 0–100. Higher PSPRS scores indicate higher degrees of disease severity, with higher functional impairment. Previous studies that utilized the PSPRS as a primary endpoint indicate annual increases in the total PSPRS score between 10 and 12. A reduction of progression in PSP by ~40%

is considered clinically meaningful (Donker Kaat et al. Parkinsonism Relat Disord 2018; 56: 98–101).

In a particular embodiment, the present invention results in a slowing of disease progression as measured by the PSP-Rating Scale, wherein said reduction of disease progression is obtained for at least one of the indices selected from the PSP-Rating Scale. In a further particular embodiment, said reduction of disease progression is at least 20%, at least 25%, at least 30%, at least 35% or at least 40% according to the PSP-Rating Scale.

Alternatively, the Combined Assessment of Function and Survival (CAFS), which is based on the Joint Rank Test, and originally developed for the analysis of function adjusted for mortality in amyotrophic lateral sclerosis (ALS), may be a further useful tool to measure disease progression in PSP. In the current setting, CAFS would rank patient clinical outcomes based on survival time and change in the PSP-Rating Scale. Consequently, in a further embodiment the subject treated achieves a reduction in disease progression according to the Combined Assessment of Function and Survival with respect to PSP.

The Schwab and England ADL (Activities of Daily Living) scale (also known as SEADL scale) is a method of assessing the capabilities of people with impaired mobility. The scale uses percentages to represent how much effort and dependence on other people need to complete daily chores. The rating may be given by a professional or by the person being tested. In a further particular embodiment wherein PSP is treated the subject treated achieves a slowing of disease progression as measured by the SEADL scale.

As described above, one of the features of PSP is progressive brain atrophy. Therefore, in a further alternative embodiment, the subject treated achieves a reduction in the progression of brain atrophy. Measurement of brain atrophy is performed routinely by a person of ordinary skill in the art with available techniques in a neurology unit, such as for example by Volumetric MRI or Computed Tomography (CT) scan. In a further alternative embodiment, the subject treated achieves a reduction in the progression of brain atrophy as measured by Volumetric MRI. Alternatively, in another particular embodiment the treated subject achieved a reduction in the progression of brain atrophy as measured by CT scan.

In another particular embodiment of the invention the tauopathy is Alzheimer's disease. Typically, three stages of Alzheimer's disease are recognized: early stage or mild AD, middle stage or moderate AD and late stage or severe AD, according to the severity of symptoms.

Therefore, in a particular embodiment of the method of the invention the tauopathy is early AD (prodromal and mild). In another it is moderate AD. In another it is severe AD. In one embodiment, the invention slows or stops progression from one of those forms of AD to a more severe form.

Alzheimer's disease is considered a secondary tauopathy, where the degree of tau accumulation in the brain appears to correlate with cognitive decline, highlighting the relevance of tau in this disease. Cognitive decline in Alzheimer's disease may be determined according to a number of established rating tools including the Clinical Dementia Rating, Alzheimer's disease assessment scale-cognitive subscale, Amsterdam-Instrument Activities of Daily Living Questionnaire, Repeatable Battery for the Assessment of Neuropsychological Status, Alzheimer's disease Cooperative Study-Activities of Daily Living, Mini-Mental State Examination, Alzheimer's disease Composite Score, or Integrated Alzheimer's disease Rating Scale. Accordingly, in one embodiment, the invention results in a slowing of disease progression according to any one of the above tools. These tools are used to both help diagnose the disease but also to monitor disease progression.

The CDR (Clinical Dementia Rating) scale is a clinician-rated dementia staging system that tracks the progression of cognitive impairment in 6 categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Each category is scored on a 5-point scale in which None = 0, Questionable = 0.5, Mild = 1, Moderate = 2, and Severe = 3. The global CDR score is established by clinical scoring rules and has values of 0 (no dementia), 0.5, (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR-SB (CDR Sum of Boxes) is obtained by adding the ratings in each of the 6 categories and ranges from 0 to 18 with higher scores indicative of greater impairment; it typically provides more information in cases of mild dementia than the global CDR score. The CDR/CDR-SB is administered to the patient and informant separately by a trained rater and takes approximately 40 to 75 minutes.

The Alzheimer's Disease Assessment Scale-Cognitive Subscale or ADAS-Cog14 is a composite scale (neuropsychological test battery and clinician reported outcome) that evaluates memory, orientation, attention, reasoning, language, and constructional praxis. Higher scores indicate greater impairment, with a minimum of 0 and a maximum of 90. The ADAS Cog14 is administered to the patient by a trained rater and takes approximately 30-45 minutes.

The Amsterdam-Instrumental Activities of Daily Living Questionnaire or A-iADL, is an adaptive and computerized observer-reported outcome measure designed to assess impairments in instrumental activities of daily living (iADL) in early dementia. The questionnaire is administered to an informant such as a relative or friend, with every effort made to use the same informant for a particular study participant throughout the study. The questionnaire consists of 70 items in 7 categories, which takes approximately 20 to 25 minutes to complete. The A-iADL assesses impairments in a broad range of daily activities including household activities, household appliances, finances, work, computer, appliances, leisure activities. The scoring range is 20 to 80 using an item response theory algorithm, with higher scores indicating better functioning. The A-iADL will be administered by a trained rater.

The Repeatable Battery for the Assessment of Neuropsychological Status or RBANS is a neuropsychological test battery that was developed for screening dementia.

The RBANS consists of 12 subtests, which give 5 Index scores, one for each of the five domains tested, and a Total Scale Score:

- Immediate memory (range: 40 to 152);
- Visuospatial/constructional (range: 50 to 136);
- Language (range: 40 to 137);
- Attention (range: 40 to 154);
- Delayed memory (range: 40 to 137); AND
- Total Scale Score (range: 40 to 160).

Index scores have a mean of 100 and a standard deviation (SD) of 15, all of which are corrected for age and education.

RBANS is administered to the patient by a trained rater and takes approximately 30 to 45 minutes to administer.

The Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) is an observer (informant)-reported outcome measure that assesses impairments in basic activities of daily living (bADLs) and iADLs. The ADCS ADL is a 23-item scale that includes 6 bADL items and 17 iADL items (the 17 items used in Integrated Alzheimer's Disease Rating Scale [iADRS]) that score from 0 to 78, with a lower score indicating greater severity. The ADCS-ADL is administered by a trained rater and takes approximately 30 to 45 minutes to complete.

The Mini-Mental State Examination or MMSE is an 11-item neuropsychological test that

is used to assess cognitive status in adults, and can be used to screen for cognitive impairment and to estimate severity of cognitive impairment. It assesses orientation, memory, attention, ability to name, ability to follow verbal and written commands, ability to write a sentence and to copy a drawing. The MMSE is administered by a trained rater and takes approximately 10 to 15 minutes to complete. The score ranges from 0 to 30. Lower scores are indicative of poorer cognitive performance.

The Alzheimer's Disease Composite Score (ADCOMS) was developed for patients with amnestic MCI due to AD and mild AD. The ADCOMS is a composite score that includes 2 MMSE items, 6 CDR-SB items, and 4 ADAS Cog14 subscales and is considered to be more sensitive to change and treatment effects than individual study instruments. There is no action for the site/Investigator to perform to achieve collection of the ADCOMS.

The ADAS-Cog14 may be combined with the ADCS-ADL score to form the iADRS or Integrated Alzheimer's Disease Rating Scale. The iADRS is a linear combination of the ADAS-Cog14 and the instrumental items of the ADCS-ADL.

iADRS = [-1(ADAS-Cog14) + 90] + iADL

The total range of the iADRS is 0 to 146, with lower scores indicating worse performance. The iADRS has been shown to be composed of 2 principal components, cognition, and instrumental function. It has been shown to be more responsive to disease progression in MCI and AD than previous versions of the ADAS-Cog, or the ADAS Cog14 alone. There is no action for the site/Investigator to perform to achieve collection of the iADRS.

Mitochondrial impairment can also be a feature of taupoathies. In one embodiment, treatment with an antibody or antigen-binding fragment thereof of the present invention may help restore mitochondrial function in a tauopathy. For example, in such tauopathies mitochondrial membrane potential may be affected, and treatment with an antibody or antigen-binding fragment thereof may help restore mitochondrial membrane potential to, or towards, normal levels. In one embodiment, the subject to be treated is one that displays mitochondrial dysfunction. In one embodiment, the subject may be one who displays altered mitochondrial membrane potential. In one embodiment, the subject displays lowered membrane potential. In a particular embodiment, the subject displays raised membrane potential and in particular displays such raised membrane potential and has a 10+16 MAPT mutation. In one embodiment, such a subject may display excess 4R tau protein isoforms. In another embodiment, the subject has a P301L mutation and in particular

may display hyperpolarised mitochondrial membranes. In one embodiment, employing the invention may mean that mitochondrial membrane potential may return, or at least be closer to, normal.

Definitions

In order that the present invention may be more readily understood, certain terms are defined below. In the absence of a definition, terms may be construed as they would be by the skilled person working in the present technical field.

Where the term "comprising" is used in the present description and claims, it does not exclude other elements. For the purposes of the present disclosure, the term "consisting of" is considered to be a preferred embodiment of the term "comprising of". If hereinafter a group is defined to comprise at least a certain number of embodiments, this is also to be understood to disclose a group which preferably consists only of these embodiments. Also provided are embodiments, consisting essentially of what is set out.

For the purposes of the present disclosure, the term "obtained" is considered to be a preferred embodiment of the term "obtainable". If hereinafter e.g. an antibody is defined to be obtainable from a specific source, this is also to be understood to disclose an antibody which is obtained from this source.

Where an indefinite or definite article is used when referring to a singular noun, e.g. "a", "an" or "the", this includes a plural of that noun unless something else is specifically stated. The terms "about" or "approximately" denote an interval of accuracy that the person skilled in the art will understand to still ensure the technical effect of the feature in question. The term typically indicates deviation from the indicated numerical value of ±10%, and preferably of ±5%.

As used herein, the terms "treatment", "treating" and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of slowing the progression or, obtaining a partial or complete cure for a disease and/or adverse effect attributable to the disease. Treatment thus covers any treatment of a disease in a human subject, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. The present

disclosure sets out various approaches for assessing tauopathy patients, including in particular for assessing PSP and AD.

Numbered further embodiments

[1] A tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or antigen-binding fragment thereof, wherein the tau-binding antibody or antigen-binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

[2] The tau-binding antibody or antigen-binding fragment thereof for use according to [1], wherein the dose or doses are each 45 mg/kg to 90 mg/kg of the tau-binding antibody or antigen binding fragment thereof.

[3] The tau-binding antibody or antigen-binding fragment thereof for use according to [1] or [2], wherein the dose or doses are each 40 mg/kg to 50 mg/kg of the tau-binding antibody or antigen-binding fragment thereof and are optionally about 45 mg/kg of the antibody or antigen-binding fragment thereof.

[4] The tau-binding antibody or antigen-binding fragment thereof for the use according to any one of [1] to [3], wherein the dose or doses are each 85 mg/kg to 95 mg/kg of the tau-binding antibody or antigen- binding fragment thereof and are optionally about 90 mg/kg of the antibody or antigen-binding fragment thereof.

[5] The tau-binding antibody or binding fragment thereof for use according to any one of [1] to [4], wherein a plurality of doses of the tau-binding antibody or antigen-binding fragment are administered wherein the interval between each pair of doses is 3 to 5 weeks.

[6] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [5], wherein a plurality of doses of the tau-binding antibody or antigen-binding fragment are administered wherein the interval between each pair of doses is 4 weeks.

[7] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [6], wherein the tau-binding antibody or antigen-binding fragment thereof is administered to the human subject in need thereof for at least 12 weeks, at least 24 weeks, at least 52 weeks, at least 68 weeks or at least 80 weeks.

[8] The tau-binding antibody or antigen-binding fragment thereof according to any one of [1] to [7], wherein the tau-binding antibody or antigen-binding fragment thereof binds to an epitope comprising the amino acid residues of S238, A239, S241, T245, A246, of SEQ ID No.: 11, optionally wherein the epitope further comprises one or more residues selected from S235, S237, K240, R242, L243, Q244, V248, and M250 of SEQ ID No.: 11.

[9] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [8], wherein the tau-binding antibody or antigen-binding fragment thereof binds to both soluble human and paired helical filaments (PHF) of human tau.

[10] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [9], wherein the tau-binding antibody or antigen-binding fragment thereof comprises

a light chain variable region comprising SEQ ID No.: 7, and

a heavy chain variable region comprising SEQ ID No.: 8.

[11] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [10], wherein the tau-binding antibody or antigen-binding fragment thereof comprises

a light chain comprising SEQ ID No.: 9, and

a heavy chain comprising SEQ ID No.: 10.

[12] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [11], wherein the tau-binding antibody or antigen-binding fragment thereof is a monoclonal humanized antibody.

[13] The tau-binding antibody or antigen-binding fragment thereof for use to any one of [1] to [12], wherein the tau-binding antibody or antigen-binding fragment thereof is administered intravenously.

[14] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [13], wherein the tauopathy is selected from progressive supranuclear palsy (PSP), corticobasal degeneration and Alzheimer's disease (AD).

[15] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [14], wherein the tauopathy is Alzheimer's disease (AD), optionally wherein the subject treated achieves a slowing of disease progression as measured by Clinical Dementia Rating score, Clinical Dementia Rating Memory Box, the delayed recall domain of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), or mini-mental state examination (MMSE)

[16] The tau-binding antibody or antigen-binding fragment thereof for use according to any one of [1] to [15], wherein the tauopathy is progressive supranuclear palsy (PSP), optionally wherein the method achieves a slowing of disease progression as measured by the PSP-Rating Scale.

[17] Use of a tau-binding antibody or antigen-binding fragment thereof in the manufacture of a medicament for the treatment of a tauopathy, wherein at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or binding fragment thereof is administered to a human subject in need thereof, wherein the tau-binding antibody or binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

EXAMPLES

EXAMPLE 1: Studies in healthy volunteers

UP0047 was a Phase 1, first-in-human, placebo-controlled, participant-blind, investigator blind, single-dose, dose-escalation study of intravenous (iv) bepranemab in healthy participants (NCT03464227). The study was conducted in Germany. The present Example describes a further study in healthy patients, UP0065. The primary objective of UP0065 was to assess the safety, tolerability and serum PK of a single-dose of bepranemab in healthy Japanese study participants, in order to determine whether these differed from the safety, tolerability and PK assessments in Caucasian participants in UP0047. An exploratory objective of the study was to assess the incidence and emergence of ADAs in serum (immunogenicity).

In the UP0047 study, a total of 258 participants were screened, and of these, 52 participants were randomized to either receive bepranemab or placebo (bepranemab 0.3mg/kg: N=2; 1mg/kg: N=6; 3mg/kg: N=6; 10mg/kg: N=6; 30mg/kg: N=6, 60mg/kg; 120mg/kg: N=6 and placebo: N=14; Figure 1a). The main reason for screen failure was ineligibility (139 participants [53.9%]), and all 52 participants completed the study.

In the UP0065 study, a total of 49 participants were screened, and 24 of these participants were randomized to receive either bepranemab or placebo (bepranemab 30mg/kg: N=6; 60mg/kg: N=6; 120mg/kg: N=6; placebo N=6; Figure 1b). The main reason for screen failure was ineligibility (15 participants [30.6%]), and all 24 participants completed the study.

Dose proportionality was observed for both Cmax and AUC across the dose range 30-120 mg/kg in both studies.

EXAMPLE 2: Studies in PSP patients

Introduction & Methods

PSP003 is a randomised, double-blind, placebo-controlled, phase 1b study designed to primarily assess the safety and tolerability of bepranemab in 25 study participants with PSP (NCT04185415). The study was conducted in a hospital setting across 13 centres in Belgium, Spain, Germany, and the UK. Study participants received either intravenous (iv) 90 mg/kg

bepranemab or a matching volume of placebo at each infusion time point, once every four weeks over a 52-week treatment period, for a maximum of 13 infusions per study participant.

Blood and CSF samples were collected to measure concentrations of bepranemab, anti-drug antibodies and for biomarker research (Figure 3). Lumbar punctures were performed before dosing. CSF sampling was carried out at baseline and day 7 (with a 14-day window in between); each CSF sample was split into aliquots for PK analyses, biomarker analyses, quality control, and biorepository samples (if consent was provided). Blood samples for coagulation parameters and platelets counts were taken and the results were evaluated before the lumbar puncture. Blood draws were performed via venipuncture and the sample divided into two aliquots for PK analyses. Post-dose PK samples were only collected for the first two infusions; for all subsequent infusions only trough samples were taken.

The Progressive Supranuclear Palsy rating scale (PSPRS) was used to measure clinical disability and disease severity of study participants at timepoints specified in Figure 3. PSPRS was an exploratory endpoint and the study was not powered to determine differences between treatment groups.

Serial structure brain MRIs were performed to detect eventual emergent alterations in brain structure at timepoints specified in Figure 3. At any time during the study, additional brain MRIs or MRI sequences may have been performed in any study participant if deemed appropriate by the Investigator/local radiologist.

Safety and tolerability of bepranemab in study participants with PSP

Overall, most Adverse Events were non-serious, mild or moderate in intensity. All Serious Adverse Events were assessed as non-related to bepranemab. No consistent or clinically relevant treatment-related patterns were observed in this study for any hematology, clinical chemistry, vital signs, ECG (electrocardiogram) or C-SSRS (Columbia-suicide severity rating scale) findings. There has been no evidence of neuroinflammatory findings on safety MRI (magnetic resonance imaging). Overall, no new safety signals were identified.

Figures 4 and 5 summarise the treatment-emergent adverse events (TEAEs) from baseline to last visit and most frequent TEAEs observed in PSP003.

Serum concentrations of bepranemab (PK)

For participants who received at least 5 consecutive doses of bepranemab, steady state was achieved by approximately Week 12.

Free tau species targeted by bepranemab in the CSF

In this assay, the term "bepranemab-tau" refers to those species of tau present in the CSF containing the epitopes for both bepranemab and the detection antibody.

The baseline (pre-dose) value of free bepranemab-tau species was taken as the 100% value, and this was used to assess the reduction of measured tau species. In other words, the term 'free' indicates tau species that have not been bound by bepranemab and are still detectable in the assay. Hence, before bepranemab treatment, all bepranemab-tau species are free and after treatment, only a proportion will remain free, depending on the administered dose of bepranemab.

The percentage of change in free bepranemab-tau from baseline to week 1 was measured for all participants (Figure 7).

In the bepranemab group, the concentrations of free bepranemab-tau in CSF changed from baseline to week 1 as follows: four participants (26.7%) had 25-100% of baseline free tau, nine participants (60.0%) had 10-25% of baseline free tau, and two participants (13.3%) had 0-10% of baseline free tau.

In the bepranemab group, the mean (SD) percent change from baseline of free bepranemab-tau levels in CSF was -80.41% (12·14) compared with -8.42% (19·97) in the placebo group (figure 6). The approximate 80% reduction of mean free bepranemab-tau levels in CSF was observed in the bepranemab group, suggesting high bepranemab target occupancy in CSF.

This determination of free bepranemab-tau was derived on an individual subject basis and is shown in Figure 8.

PSP-Rating Scale

As mentioned above, the study was not powered to determine differences between treatment groups. However, there is a difference in the bulbar domain rating (relating to speech and swallowing) between study arms, that appears consistently across different analysis approaches. See table:

Table 2

	Difference in Means (CI)*	p-value from Wilcoxon test
Bulbar	0.0733 (-0.0166, 0.1632)	0.0823

**CI is based on the assumption that the data is normally distributed.*

Hence, despite the small sample size it appears that bepranemab has achieved a statistically significant change in decline rate at the 10% significance level in at least one of the PSP-Rating Scale's indices. No adjustment for multiplicity was performed.

Example 3: Studies in patients with Alzheimer's disease

AH0003 (NCT04867616) is a global, multicenter, patient-blind, investigator-blind, placebo-controlled, parallel-group study, investigating the efficacy, safety, and tolerability of bepranemab (administered intravenously, every 4 weeks) versus placebo in patients with prodromal (40%) or mild (60%) AD over an 80-week treatment period, followed by an optional 48-week open-label extension (OLE). The primary objective is the change from baseline to Week 80 in the Clinical Dementia Rating (CDR) Scale Sum of Boxes total score. Secondary objectives include: pharmacokinetics (PK); safety and tolerability; the effect of bepranemab on tau positron emission tomography (PET) imaging at Weeks 56 and 80; and the changes from baseline in the 14-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14), Amsterdam-Instrumental Activities of Daily Living, and Mini-Mental State Examination (MMSE) at Weeks 56 and 80. The OLE will assess the long-term safety and tolerability of bepranemab. Approximately 150 patients per arm will be enrolled across 3 study arms (45 mg/kg and 90 mg/kg bepranemab, and placebo; randomized 1:1:1). Eligible patients will meet the National Institute of Aging-Alzheimer's Association (NIA-AA) 2018 Stage 3 or 4 definitions of prodromal or mild AD, respectively. Patients will have a global CDR score indicative of prodromal AD (0.5) or mild AD (0.5 or 1.0) and a CDR-Memory Box score $\geq$0.5 at screening and baseline. Patients will have a score of $\leq$85 for the delayed recall domain of the Repeatable Battery for the Assessment of Neuropsychological Status, MMSE $\geq$20 at screening and must meet the NIA-AA 2018 definition of cerebral beta-amyloid (Aβ) accumulation, by either a positive centrally read PET scan or a positive cerebrospinal fluid pTau181/Aβ1-42 ratio.

Example 4: Body weight-tiered fixed dosing based on modeling & simulation

In order to model potential fixed dose similar to the 90 mg/kg dose used in the earlier Examples, a population pharmacokinetic (PopPK) model was developed based on data from study UP0047 (with i.v. bepranemab doses of 0.3-120 mg/kg were administered), which characterized the dependency of bepranemab clearance and distribution volume. Utilizing this PopPK model, PK simulations were conducted to derive fixed (gram), rather than body weight-adjusted (mg/kg), doses of bepranemab. An adult PSP population weighing 40-100 kg was selected. To avoid potential over-exposure and under-exposure in lower and higher body weight individuals, respectively, fixed doses were derived separately for body weights of less than and greater than 60 kg.

In simulations of 2000 individuals per simulation, predicted bepranemab exposures for fixed bepranemab doses of 4.8 g and 7.2 g every 4 weeks for body weights of 40-<60 kg and ≥60-100 kg, respectively, were found to be acceptably comparable to exposure for a dose of 90 mg/kg in all individuals irrespective of body weight (Figure 9). The 2 fixed doses of 4.8 g and 7.2 g provide a more patient- and clinically-suitable alternative to individual bepranemab doses based on individual body weight.

CLAIMS

1. A tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering to the human subject at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or antigen-binding fragment thereof, wherein the tau-binding antibody or antigen-binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

2. The tau-binding antibody or antigen-binding fragment thereof for use according to claim 1, wherein the dose or doses are each 45 mg/kg to 90 mg/kg of the tau-binding antibody or antigen binding fragment thereof.

3. The tau-binding antibody or antigen-binding fragment thereof for use according to claim 1 or 2, wherein the dose or doses are each 40 mg/kg to 50 mg/kg of the tau-binding antibody or antigen-binding fragment thereof and are optionally about 45 mg/kg of the antibody or antigen-binding fragment thereof.

4. The tau-binding antibody or antigen-binding fragment thereof for the use according to any preceding claims, wherein the dose or doses are each 85 mg/kg to 95 mg/kg of the tau-binding antibody or antigen- binding fragment thereof and are optionally about 90 mg/kg of the antibody or antigen-binding fragment thereof.

5. A tau-binding antibody or antigen-binding fragment thereof for use in a method of treating a tauopathy in a human subject in need thereof, the method comprising administering a fixed dose of the tau-binding antibody or antigen-binding fragment to the subject, wherein:

(a) the subject has a body weight of 40kg up to, but not including, 60kg and the fixed dose is 4.5g to 5.5g of the tau-binding antibody or antigen-binding fragment; or

(b) the subject has a body weight of 60kg to 100kg and the fixed dose is 6.5g to 7.5g of the tau-binding antibody or antigen-binding fragment,

wherein the tau-binding antibody or antigen-binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

6. The tau-binding antibody or antigen-binding fragment thereof for the use according to claim 5, wherein the subject has a body weight of 40 kg up to, but not including, 60 kg and the fixed dose is 4.8 g of the tau-binding antibody or antigen-binding fragment.

7. The tau-binding antibody or antigen-binding fragment thereof for the use according to claim 5, wherein the subject has a body weight of 60 kg to 100 kg and the fixed dose is 7.2 g of the tau-binding antibody or antigen-binding fragment.

8. The tau-binding antibody or binding fragment thereof for use according to any one of the preceding claims, wherein a plurality of doses of the tau-binding antibody or antigen-binding fragment are administered wherein the interval between each pair of doses is 3 to 5 weeks.

9. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein a plurality of doses of the tau-binding antibody or antigen-binding fragment are administered wherein the interval between each pair of doses is 4 weeks.

10. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof is administered to the human subject in need thereof for at least 12 weeks, at least 24 weeks, at least 52 weeks, at least 68 weeks or at least 80 weeks.

11. The tau-binding antibody or antigen-binding fragment thereof according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof binds to

an epitope comprising the amino acid residues of S238, A239, S241, T245, A246, of SEQ ID No.: 11, optionally wherein the epitope further comprises one or more residues selected from S235, S237, K240, R242, L243, Q244, V248, and M250 of SEQ ID No.: 11.

12. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof binds to both soluble human and paired helical filaments (PHF) of human tau.

13. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof comprises

a light chain variable region comprising SEQ ID No.: 7, and

a heavy chain variable region comprising SEQ ID No.: 8.

14. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof comprises

a light chain comprising SEQ ID No.: 9, and

a heavy chain comprising SEQ ID No.: 10.

15. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof is a monoclonal humanized antibody.

16. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tau-binding antibody or antigen-binding fragment thereof is administered intravenously.

17. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tauopathy is selected from progressive supranuclear palsy (PSP), corticobasal degeneration and Alzheimer's disease (AD).

18. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tauopathy is Alzheimer's disease (AD), optionally wherein the subject treated achieves a slowing of disease progression as measured by Clinical Dementia Rating score, Clinical Dementia Rating Memory Box, the delayed recall domain of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), or mini-mental state examination (MMSE)

19. The tau-binding antibody or antigen-binding fragment thereof for use according to any one of the preceding claims, wherein the tauopathy is progressive supranuclear palsy (PSP), optionally wherein the method achieves a slowing of disease progression as measured by the PSP-Rating Scale.

20. Use of a tau-binding antibody or antigen-binding fragment thereof in the manufacture of a medicament for the treatment of a tauopathy, wherein at least one dose of 30 mg/kg to 120 mg/kg of the tau-binding antibody or binding fragment thereof is administered to a human subject in need thereof, wherein the tau-binding antibody or binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and

a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.

21. A Use of a tau-binding antibody or antigen-binding fragment thereof in the manufacture of a medicament for the treatment of a tauopathy, wherein at least one fixed dose of the tau-binding antibody or antigen-binding fragment is administered to a human subject in need thereof, wherein:

(a) the subject has a body weight of 40kg up to, but not including, 60kg and the fixed dose is 4.5g to 5.5g of the tau-binding antibody or antigen-binding fragment; or

(b) the subject has a body weight of 60kg to 100kg and the fixed dose is 6.5g to 7.5g of the tau-binding antibody or antigen-binding fragment,

wherein the tau-binding antibody or antigen-binding fragment thereof comprises:

a light chain variable region comprising a CDR1 selected from SEQ ID No.: 1, a CDR2 selected from SEQ ID No.: 2, and a CDR3 selected from SEQ ID No.: 3; and
a heavy chain variable region comprising a CDR1 selected from SEQ ID No.: 4, a CDR2 selected from SEQ ID No.: 5, and a CDR3 selected from SEQ ID No.: 6.