Statistical Analysis Plan

Interventional, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study to assess the efficacy, safety and tolerability of Lu AF82422 in patients with Multiple System Atrophy

Lu AF82422

Trial No.:	18331A (**AMULET** – Del**a**y **Mul**tiple Syst**e**m A**t**rophy)
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List of Abbreviations and Definitions of Terms

ANCOVA	Analysis of Covariance
APTS	all-patients-treated set
aUMSARS	abbreviated Unified Multiple System Atrophy Rating Scale
CI	confidence interval
DMC	Data Monitoring Committee
DTI	Diffusion-tensor imaging
eCRF	electronic case report form
EoTDBP	End of treatment double-blind period
EoTOLEP	End of treatment open-label extension period
FAS	full-analysis set
IMP	investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
ML	maximum likelihood
MMRM	mixed model for repeated measurements
MSA	multiple system atrophy
mUMSARS	modified Unified Multiple System Atrophy Rating Scale
NfL	neurofilament light chain
OC	observed case(s)
PYE	patient years of exposure
R	Open source statistical software package
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
UMSARS	Unified Multiple System Atrophy Rating Scale
vMRI	volumetric magnetic resonance imaging

1 Objectives

1.1 Primary Objective

- To evaluate the efficacy of Lu AF82422 on disease progression in patients with Multiple System Atrophy (MSA) during the Double-blind Period (DBP)

1.2 Secondary Objectives

- To evaluate the efficacy of Lu AF82422 on:
  - Function
  - Global impression, severity of illness
  - Autonomic symptoms
  - Global disability
  - Disease milestones
  - Health-related quality of life

- To evaluate the efficacy of Lu AF82422 on disease progression measured by brain Magnetic Resonance Imaging (MRI)
- To evaluate the efficacy of Lu AF82422 on biofluid biomarkers of disease progression
- To evaluate the pharmacokinetics of Lu AF82422

All during the Double-blind Period (DBP).

1.3 Safety Objectives

- To evaluate the safety and tolerability of Lu AF82422 in patients with MSA during the Double-blind Period (DBP) and the open-label extension (OLE)

1.4 Exploratory Objectives

- To explore the target engagement of Lu AF82422 to α-synuclein
- To explore the target engagement of Lu AF82422 on pathological species of α-synuclein
- To explore the relationship between UMSARS, MRI parameters and NfL
- To explore the efficacy of Lu AF82422 for up to 72 weeks of treatment on clinical scales and biomarkers
- To collect patient experience with impaired functions due to MSA to support the interpretation of change on the UMSARS (Exit Interview subset)
- To collect patient experience with study participation (Study Experience Interview subset)

All during the Double-blind Period (DBP).

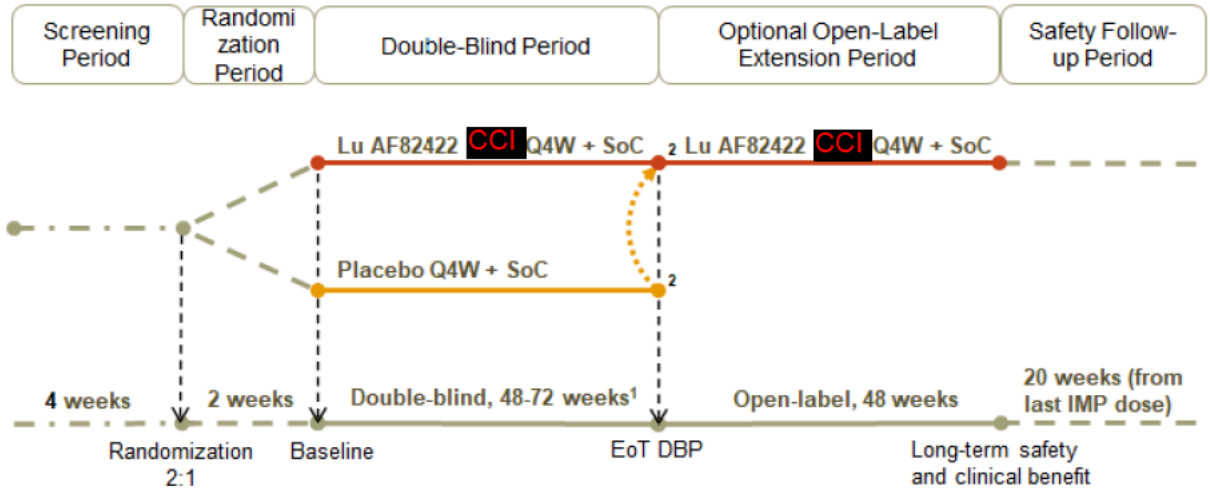
- To explore the effect of long-term treatment with Lu AF82422 during the open-label extension (OLE)

2 Study Design

- This is a phase II, interventional, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study of the efficacy (slowing disease progression), safety, and tolerability of Lu AF82422 in patients with MSA. The efficacy of Lu AF82422 is assessed using the UMSARS TS; supportive assessments include evaluation of function, global impression of severity of illness, autonomic symptoms, disability, health-related quality of life, biofluid biomarkers, and imaging.
- The target population for this study is patients with possible or probable MSA, as defined by the 2008 Gilman diagnostic criteria. The study will recruit patients with evidence of parkinsonism (MSA-P) and/or cerebellar syndrome (MSA-C). Patients will be allowed stable treatment for managing their symptoms of MSA during the study.
- The patients [N=60] will be randomized to Lu AF82422 CCI or placebo (2:1) via a centralized randomization system (Interactive Response Technology [IRT]). Two strata variables will be applied to ensure a balanced treatment allocation of Lu AF82422 and placebo: CCI [redacted] and Region (US/Japan, with a maximum of 25% of patients from Japan).
- The study duration from the Screening Visit to the Safety follow-up Visit is between 70 to 94 weeks for patients not entering the optional OLE period and between 118 to 142 weeks for patients continuing in the OLE. The study includes the following periods:
  - Screening period (4 weeks)
  - Randomization period (2 weeks)
  - Double-blind treatment period (48 weeks up to 72 weeks)
  - Optional OLE treatment period (48 weeks)
  - Safety Follow-up Period (20 weeks; will take place after last investigational medicinal product [IMP] administration)
- The individual double-blind period will vary from 48 weeks up to 72 weeks. Once the last patient will reach Week 48, this visit will be the EoTDBP Visit for that patient. Patients who have not completed the visit at Week 72 at the time of Last Patient reaches EoT will have their next visit converted to an DBP EoT Visit with assessments as listed for Visit 24, according to study procedures and assessments (Appendix IV). During the double-blind treatment period, patients will attend IMP Visits to follow a dosing schedule with either Lu AF82422 or placebo every four weeks (Q4W).
- Patients who enter the OLE will receive the first open-label dose (Visit 1E) at the same day as the EoTDBP or as soon as possible thereafter, but not later than 5 months after EoT Visit of the DBP and will be enrolled to OLE no later than end of Q1 2024.
- After the DBP EoT/ End of Open-Label Treatment/Withdrawal Visit, patients will be scheduled for a Safety Follow-up Visit 20 weeks after last IMP dose.
- An independent Data Monitoring Committee (iDMC) will regularly monitor the patients' safety and tolerability data according to the Data Monitoring Committee (DMC) Charter.

An overview of the study is presented in Panel 1.

Panel 1 Study Design



1. Variable treatment period of minimum 48 weeks up to 72 weeks of treatment. Patients who have not completed Week 72 Visit at the time Last Patient reaches Week 48, will be scheduled for the EoT DBP Visit 4 weeks after latest dose of IMP
2. Patients who do not continue in the optional Open-Label Extension will enter the Safety Follow-up Period after the EoT DBP Visit

DBP = Double-Blind Period; EoT = End of Treatment; SoC = Standard of Care; Q4W = every 4 weeks

3 Definitions

3.1 Definition of Baseline

3.1.1 Double Blind Period

The baseline value for the DBP is the value captured at the Baseline Visit (week 0). In case an assessment has not been performed at the Week 0 Baseline visit or the Week 0 value is missing or invalid, the value from the last completed pre-IMP assessment will be used as baseline.

The screening visit takes place approx. 6 weeks prior and the randomisation visit approx. 2 weeks prior the baseline visit.

3.1.2 Open-label Extension Period

The baseline value for patients who enter the OLE and who have the first visit of the OLE at the same day of the EoTDBP Visit or up to 7 days after the EoTDBP, clinical assessments performed at the EoTBDP Visit will serve as the baseline value for the OLE. For patients entering OLE >7 days after EoTDBP, the OLE baseline value is the value captured at the dedicated Visit 1E.

3.2 Definition of Periods

The study consists of the following periods:

- Screening Period (4 weeks): Screening Visit (V1) to Randomization Visit (V2)
- Randomization Period (2 weeks): Randomization Visit (V2) to Baseline DB Visit (V3)
- Double-blind Treatment Period (varying: 48 to 72 weeks): Baseline DB Visit (V3) to EoTDB Visit (V24) – Time point to be defined by IMP initiation on V3
- Optional Open-Label Treatment Period (48 weeks): from Baseline OLE Visit (V1E) to EoTOLE (V13E) - Time point to be defined by IMP initiation on V1E

Patients will subsequently after end IMP administration enter:

- Safety Follow-up Period 1 following DB (20 weeks): following the EoTDBP Visit (V24) to Safety Follow-up Visit (V25)
- Safety Follow-up Period 2 following OLE (20 weeks): following the EoTOLE Visit (V13E) to Safety Follow-up Visit (SFU-E)

Due to the late approval of the OLE protocol amendment some participants entering the OLE might have entered the first safety follow-up period prior to entering the OLE, and hence would have two safety follow-up periods.

3.3 Definition of Withdrawal

The group of patients who withdrew from treatment at the scheduled visits in the Double-blind Treatment Period will be described as *withdrawn from study*. This group will also contain randomized patients who withdrew from treatment prior to receiving any IMP and patients who died. The complementary group will be described as *completed study*. Patients who withdraw, except for those who withdraw their consent or died, will be asked to attend a Safety Withdrawal Visit 20 weeks after the last dose of IMP and undergo Safety Follow-Up evaluations.

Participants that drop out of the OLE will also undergo Safety Follow-Up evaluations according to trial procedures.

4 Endpoints

4.1 Primary Endpoint, Double-Blind Period

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) up to EoTDB

4.2 Key Secondary Endpoint, Double-Blind Period

Disease progression

- as assessed by longitudinal changes from baseline in the modified UMSARS Part I (mUMSARS) score up to EoTDB

4.3 Secondary Endpoints, Double-Blind Period

Disease progression

- as assessed by longitudinal changes from baseline in the UMSARS Part I, and UMSARS Part II scores up to EoTDB

Function

- Change from baseline to Week 48 in UMSARS TS
- Change from baseline to Week 48 in UMSARS Part I score
- Change from baseline to Week 48 in mUMSARS score
- Change from baseline to Week 48 in UMSARS Part II score
- Change from baseline to Week 48 in Schwab and England Activities of Daily Living scale (SE-ADL)

Global impression

- Change from baseline to Week 48 in Clinical Global Impression – Severity (CGI-S) score
- Change from baseline to Week 48 in Patient Global Impression – Severity (PGI-S) score
- Change from baseline to Week 48 in Observer-reported Global Impression – Severity of Illness (OGI-S)

Autonomic symptoms

- Change from baseline to Week 48 in Composite Autonomic Symptom Score Select Change (COMPASS Select Change) score

Global disability

- Change from baseline to Week 48 in UMSARS Part IV score

Disease milestones

- Change from baseline to Week 48 in speech, swallowing, falls, and walking, as assessed by the UMSARS Part I sub-items
- Change from baseline to Week 48 in frequency, cause and consequence of falls, as assessed by the fall diary in dedicated periods

Health-related quality of life

- Change from baseline to Week 48 in EQ-5D-5L score (individual items and VAS score)

MRI biomarkers

- Percentage change from baseline to Week 48 in brain volume in brain regions-of-interest (ROIs); primary ROIs: pons and cerebellum; secondary ROIs: caudate nucleus, putamen, brain stem and total grey matter, as measured by volumetric MRI (vMRI)

Biofluid biomarkers

- Blood: Change from baseline up to Week 48 in neurofilament light chain (NfL) concentrations

Pharmacokinetics

- Lu AF82422 plasma concentration during treatment and safety follow-up
- Lu AF82422 cerebrospinal fluid (CSF) concentrations and the CSF/plasma concentration ratios

4.4 Safety Endpoints

4.4.1 Double-Blind Period

- Treatment emergent adverse events
- Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and ECG parameter values
- Development of specific anti-drug antibodies (ADA)
- Findings on MRI, as specified in the *Imaging Charter*
- Columbia-Suicide Severity Rating Scale (C-SSRS) score

4.4.2 Open-label Extension Period

- Treatment-emergent adverse events
- Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, and weight parameter values
- Development of specific anti-drug antibodies (ADAs)
- Columbia-Suicide Severity Rating Scale (C-SSRS) score

4.5 Exploratory Endpoints

4.5.1 Double-Blind Period

Disease progression

- as assessed by longitudinal changes from baseline in the abbreviated UMSARS (aUMSARS) score up to EoTDB

Function

- Changes from baseline to Week 48 in aUMSARS

Autonomic symptoms

- Change from baseline to Week 48 in heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III

Disease milestones

- Time to wheelchair use, as assessed by the recording of wheelchair use in the physical examination CRF Form
- Change from baseline to Week 48 in frequency of falls, as assessed by PamSys device
- Change from baseline to Week 48 in gait parameters, as assessed by FeetMe device

MRI biomarkers

- Percentage change from baseline to Week 48 in cerebral blood flow in ROIs; putamen and cerebellum, as measured by arterial spin labelling (ASL) MRI
- Percentage change from baseline to Week 48 in tissue integrity in ROIs; primary ROIs: putamen, cerebellar cortex and white matter; secondary ROIs: caudate nucleus, globus pallidus and middle cerebellar peduncle, as measured by diffusion-tensor imaging (DTI) MRI

Blood/CSF biomarkers

- CSF: Change from baseline up to Week 48 in t-tau and NfL concentrations
- CSF: Concentrations of 'free' and 'total' α-synuclein at baseline and Week 48
- CSF: Changes from baseline up to Week 48 in pathological species of α-synuclein
- Blood: Plasma concentrations of 'free' and 'total' α-synuclein during treatment and safety follow-up

4.5.2 Open-label Extension Period

Effect on long-term treatment:

- Change from baseline of the DBP and baseline of the OLE to End-of-Treatment of the OLE (EoTOLE) in UMSARS TS and mUMSARS score
- Change from baseline of the DBP and baseline of the OLE to EoTOLE in CGI-S score
- Change from baseline of the DBP and baseline of the OLE to EoTOLE in PGI-S score
- Change from baseline of the DBP and baseline of the OLE to EoTOLE in SE-ADL score
- Change from baseline of the DBP and baseline of the OLE to EoTOLE in health-related quality of life, as assessed using EQ-5D-5L score
- Percentage change from baseline of the DBP and baseline of the EoTOLE in brain atrophy in ROIs, as measured using vMRI
- Change from baseline of the DBP and baseline of the OLE to EoTOLE in blood NfL concentrations

5 Analysis Sets

The patients will be assigned to analysis sets based on IMP intake and post-baseline assessments of the primary efficacy variable in the Treatment Period.

The following analysis sets will be used for the analyses:

- *all-patients-randomized set* (APRS) – all randomized patients
- *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of double-blind IMP
- *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the UMSARS TS, prior to, or at withdrawal from treatment
- *PK sub-set* (PKS) – all patients in the APTS with quantifiable plasma or CSF concentration of Lu AF82422
- *Sensor-based subset* (SBS) – all patients in the APTS who consented to wear at least one of the included sensor-based devices and who had a valid baseline assessment and at least one valid post-baseline assessment, where 'valid assessment' covers that gait parameters can be derived within the observation period
- *Exit Interview subset* - all patients in the FAS having a complete Exit interview with the patient and/or the caregiver
- *Study Experience subset* - all patients in the FAS having a complete Study Experience interview with the patient and/or the caregiver
- *Open-label treatment extension set* (OLES) – all patients in the FAS who consented to participate in the OLE and who had at least one dose of Open-Label IMP for the OLE

All data from the Placebo-controlled Period will be cleaned and the database for the DB-Period will be locked when there are no more patients in the DB-Period. The patients and data will be classified into the analysis sets according to these definitions at a Classification Meeting held after the database containing all efficacy measures from the DB-Period has been released but before unblinding of the study.

Demographics, baseline characteristics and baseline efficacy variables will be summarized based on the APTS and on the OLES, respectively.

The efficacy analyses for the DB-Period will be based on the FAS. Analyses for the Extension Period will be based on the OLES.

Safety outputs (including exposure and concomitant medications) will be based on APTS in the DB-Period and OLES for the Extension Period, respectively. Relevant safety outputs for data collected during the Safety Follow-up Period for participants not entering the OLE will be based on the APTS.

Listings will be based on the APTS.

6 Descriptive Statistics

Unless otherwise specified, summary statistics (n, arithmetic mean, standard deviation [SD], median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables, and counts and, if relevant, percentages will be presented for categorical variables. Shift-tables will be presented for categorical variables where specified.

Unless otherwise specified, data listings will include site, treatment group, patient number, sex, age, region and race.

7 Patient Disposition

7.1 Summary of Patient Disposition

Patient disposition will be summarized overall and by region. Summaries will include the number of patients in each analysis set defined in chapter 5, and the number of patients in the APTS who completed or withdrew from study.

The number of patients with a completed OLE and Safety Follow-up visit will be presented.

7.2 Withdrawals

The number of patients who withdrew from the study will be summarized by primary reason for withdrawal and all reasons for withdrawal by period.

If relevant, Kaplan-Meier failure plots of time to withdrawal will be presented by treatment group for the DB-Period. The time will be calculated from the date of first dose of IMP to the date of withdrawal in the DB-Period. Patients who completed the DB-Period according to their individual treatment duration (48-72 weeks) will be regarded as censored at the End of treatment visit.

Patients who withdrew from the study will be listed and the listing will include the number of days in the study until withdrawal, the number of days on IMP, the primary reason for withdrawal, and all reasons for withdrawal.

All tables, graphs, and listings will be based on the FAS.

8 Demographics and Baseline Characteristics

Demographics (sex, age, race, region), Screening MRI findings supporting MSA diagnosis and CCI [redacted]; baseline disease characteristics (incl. MSA sub-type, CSF/blood NfL level, result from the qualitative alpha-synuclein seeding assay (SAA), time since symptom onset and diagnosis); baseline physical examinations and baseline efficacy variables will be summarized by treatment group and overall.

Concurrent as well as relevant past medical and psychiatric disorders will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) and summarized.

A concurrent medical or psychiatric disorder is a disorder that is ongoing at the baseline Visit. A past medical or psychiatric disorder is a disorder that ended prior to the baseline Visit.

Demographics and baseline characteristics will be summarized based on the APTS, PKS and SBS, and baseline efficacy variables will be summarized based on the FAS.

9 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the *WHO Drug Dictionary* (WHO-DDE).

Medications will be classified according to the start and stop time and summarized by anatomical therapeutic chemical (ATC) code, and generic drug name:

- medication discontinued prior to first dose of IMP
- concomitant medication continued after first dose of IMP
- concomitant medication started at or after first dose of IMP

In addition, concomitant medications continued or started after first dose of IMP will classified into two overall groups depending on purpose, i.e., treatment of motor symptoms (‘anti-Parkinson medication’) and treatment of autonomic dysfunction (‘Autonomic dysfunction medication’). The classification will be done prior to unblinding according to Protocol Appendix VII.

The tables will be based on the APTS.

10 Exposure

For each infusion visit, information related to infusion completed as planned (yes/no), infusion temporarily interrupted (yes/no), and infusion lasted longer than 30 (+10) minutes (yes/no), as well as descriptive statistics for the duration of infusions (this duration includes duration of any infusion interruptions) and duration of temporary interruptions will be summarized by treatment group for the DB-Period and the OLE-Period, respectively.

Patients, who at any point during the study received a different dose than what was planned, will be listed for each period. The listing will include date of infusion visit, planned dose for the patient and actual dose received for the patient.

Exposure (days) to IMP will be calculated as:

(Date of last dose + 28 days) – Date of first dose + 1

Exposure to IMP will be summarized in weeks using descriptive statistics.

Patient years of exposure (PYE) will be calculated as the sum of the number of days of exposure to IMP for each patient, divided by 365.25 days.

The number and percentage of patients with different durations of exposure (≤4 weeks, >4 to ≤8 weeks, >8 to ≤12 weeks, …, >68 to ≤72 weeks) will be presented.

Exposure will be summarized based on the APTS. In addition, all infusion data will be listed.

11 Fall Diary Compliance

The Fall Diary is planned to be dispensed and filled out in 5 periods during the study, i.e., at a two-week Baseline period and at four post-baseline four-week periods, respectively. For each period, days where the fall diary has been missed will be summarized and presented by period and treatment group. Furthermore, the number of patients missing 7 days or more (at Baseline and at subsequent periods) and 14 days or more (at subsequent periods) in each period will be presented by period and treatment group.

A day where the fall diary has been missed is defined as a day where the subject did not fill out anything in the diary.

The summaries will be based on the FAS.

12 Wearable Compliance

For both Baseline and the DB-Period, compliance is evaluated as number of days used for each of the two wearables, i.e., FeetMe and PanSys, which will be summarized within each interval where applied and treatment group. Furthermore, the number of patients missing 7 days or more and 14 days or more in a 28-day period will be presented by interval and treatment group. The following intervals will be evaluated:

- BL interval: V2 to V3 (2 weeks)
- Interval 1: V7 to V9 (4 weeks)
- Interval 2: V10 to V11 (4 weeks)
- Interval 3: V13 to V14 (4 weeks)
- Interval 4: V17 to V18 (4 weeks)

Records outside the above predefined intervals will be included as long as they can be mapped to one of the above intervals according to the defined visit windows (See section 24.2). Individual wearable data will be mapped to the end visit defining each interval, corresponding to the visit where the wearable is handed back.

The summaries will be based on the SBS.

13 Primary Estimand

The following primary estimand is defined as:

CCI

Proposed handling of IE's

CCI

For evaluating the appropriateness of this overall strategy, a number of sensitivity analyses will be performed using different imputation strategies for missing data. For additional information see section 14.3.5: Sensitivity Analyses of the Primary Endpoint, also covering sensitivity analyses for the key Secondary Endpoint.

Key Secondary Estimand

A key secondary study estimand will be defined in a similar manner with the endpoint of interest being the CCI

14 Efficacy

14.1 Overview of Planned Efficacy Analyses in the DB-Period

An overview of all planned efficacy analyses is provided in Panel 2. Where relevant, the analyses will be presented by visit. Endpoints related to as 'disease progression' (primary and selected secondary endpoints) will be analysed using a 'Bayesian' progression model; remaining continuous variables will be analysed applying a MMRM in a Frequentist framework, where stated.

Panel 2 Overview of Planned Efficacy Analyses (DB-Period)

Variables	Type	Priority	Description
UMSARS TS	1	1	Sum of UMSARS Part I+II items (Primary)
mUMSARS score	1	2	Sum of Part I items with respond option 0 and 1 collapsed
UMSARS Part I score	1	3	Sum of UMSARS Part I items
UMSARS part II score	1	3	Sum of UMSARS Part II items
aUMSARS score	1	4	Sum of UMSARS Part I+II selected items - PI: 1,3,4,7,8 & PII: 2,6,8,11,14
SE-ADL score	2	3	Schwab and England Activities of Daily Living scale: sum of items
CGI-S score	2	3	Global impression severity, Clinical: sum of items
PGI-S score	2	3	Global impression severity, Patient: sum of items
OGI-S score	2	3	Global impression severity, Observer-reported: sum of items
COMPASS select change	2	3	Composite autonomic symptom: a score for each domain
UMSARS part III items	2	4	Heart rate, sys/dia blood pressure; individual items
UMSARS part III items	3	4	orthostatic symptoms; individual item
UMSARS part IV item	3	3	Global disability: UMSARS single item
UMSARS part I items	3	3	Disease milestones: Speech, swallowing, walking and falls; UMSARS Part I single items
Patient fall diary	3	3	Disease milestones: Frequency, cause and consequence of falls; patient dairy derived
Use of wheelchair	4	4	Disease milestones: Wheelchair – time to full time user; according to physical examination
PamSys digital device	3	4	Disease milestones: Frequency of Falls; PamSys derived
FeetMe digital device	2	4	Disease milestones: gait parameters; FeetMe derived
EQ-5D-5L items	3	3	Health-related quality of life: domain scores
EQ-5D-5L VAS score	2	3	Health-related quality of life: VAS score
MRI, volumetric (vMRI)	2	3	volume in ROIs (e.g., caudate nucleus, putamen, striatum, pons, brain stem, grey matter and cerebellum)

Variables	Type	Priority	Description
MRI, diffusivity (DTI MRI)	2	4	Mean diffusivity in ROIs (e.g., caudate nucleus, putamen, globus pallidus, pons, cerebellar cortex and white matter and middle cerebellar peduncle, both FA and MD)
Blood biomarkers	2	3, 4	neurofilament light (NfL) concentrations [2], 'free' and 'total' α-synuclein [3]
CSF biomarkers	2	4	concentrations of t-tau, NfL, 'free' and 'total' α-synuclein, pathological species of α-synuclein
MRI, arterial spin (ASL)	2	4	Mean Cerebral blood flow in ROIs (e.g., putamen and cerebellum)

Type: 1 = continuous_Bayes; 2 = continuous_Other; 3 = categorical; 4 = time to event; Priority: 1 = Primary; 2 = Key Secondary; 3 = Secondary; 4 = Exploratory

14.2 General Efficacy Analysis Methodology

Unless otherwise specified, all efficacy analyses will be based on the FAS for the observed case (OC) data.

For endpoints analysed in the Bayesian framework, the success threshold for the Bayesian posterior probability of superiority relative to placebo [Prob(θ<1)] has been calibrated using simulations to correspond to a significance level of 5% applied one-sided. By doing so a success threshold of 0.975 has been identified which will be used to evaluate the primary endpoint and remaining endpoints evaluated by the Bayesian progression model. A burn-in of 1000 samples will be used for the Bayesian analysis.

All statistical tests of the secondary efficacy endpoints will be presented two-sided on a 5% significance level.

A testing strategy will be applied including the primary analysis on UMSARS TS and the key secondary analysis on mUMSARS to protect the type I error on an overall one-sided 5% significance level for these analyses. Further details to be found in chapter 15.

For analysis of exploratory efficacy data collected in the open-label extension, the original placebo patients will be presented as a separate group and hence there will be no pooling of treatment groups.

14.3 Analysis Methodology for the Primary Endpoint

14.3.1 Primary Analysis of the Primary Endpoint

The primary efficacy analysis following up to 72 weeks of treatment will be based on a Bayesian repeated measures model, also referred to as a Bayesian functional-impairment

progression model (BFPM), of the changes from baseline in the UMSARS TS. The BFPM incorporates the following aspects:

- Repeated measures for the change from baseline in the UMSARS TS score over the recurring 72-week's visit schedule
- Piece-wise linear rate of progression per 12-week time interval. However, does not require equally spaced intervals between observations. Time modelled continuously
- Patient-level random effect in rate of progression
- Proportional treatment effect, θ, for slowing of disease progression rate when treated relative to placebo. In particular, if θ<1, the active treatment slows the rate of progression relative to placebo. If θ>1, the active treatment increases the rate of progression relative to placebo. If θ=1, the rate of progression of UMSARS TS is the same for both active treatment and placebo
- Fixed multiplicative covariate effects in the increase or decrease in the overall rate of progression of UMSARS TS for categorized CCI [redacted] and region (US and Japan) common across all visits
- Prior distributions for model parameters selected in a conservative and non-informative manner using relatively large outcome spaces
- The primary analysis considers only actual observations and does not impute missing data

Let change from baseline in the UMSARS TS at visit j for subject i be labelled $Y_{i,j}$, $i = 1, \dots, N, j = 1, \dots, J_i$ where there are J_i total post-baseline visits for subject i. Change from baseline will be modelled as piece-wise linear with time intervals, $k = 1, \dots, K$, defined every 12 weeks. Let $X_{i,j,k}$ be the exposure (time since baseline in weeks) for subject i at visit j during the time interval k. The MSA progression model is:

$$Y_{i,j} \sim N\left(\mu_{i,j}, {\sigma_{t(i)}}^2\right); i = 1, \dots, N; j = 1, \dots, J_i$$

$$\mu_{i,j} = 0 + \sum_{k=1:K} \left(\beta_k + \beta_{k,i}\right) * (X_{i,j,k}/12) * \theta_{t(i)} * \exp\left(\delta_{g(i)} + \eta_{r(i)}\right)$$

where each parameter is defined below and the prior distribution for the parameter is given:

β_k: Mean expected change from baseline over each 12-week interval

$$\beta_k \sim Norm\left(0, 10^2\right); k = 1, \dots, K$$

$\beta_{k,i}$: Subject-level additive random effect in change from baseline over each 12-week interval for subject i

$$\beta_{k,i} = \beta_i;\ \beta_i \sim Norm(0, \sigma_\beta^2);\ \ \sigma_\beta \sim Unif(0,20)$$

θ_t: Multiplicative proportional slowing in rate of progression for treated (t=2) relative to placebo (*t=1*).

$$\theta_1 = 1; \quad \theta_2 \sim Unif(0,2)$$

δ_g: Multiplicative fixed covariate effects for the increase or decrease in rate of progression for plasma NfL level, i.e., missing (g = 3) and high (g = 2) relative to low (g = 1) common across all visits

$$\delta_1 = 0; \quad \delta_2 \sim Normal(0,10^2); \quad \delta_3 \sim Normal(0,10^2)$$

η_r: Multiplicative fixed covariate effects for the increase or decrease in rate of progression for regions, i.e., Japan (r = 2) relative to US (r = *1*) common across all visits

$$\eta_1 = 0; \quad \eta_2 \sim Normal(0,10^2)$$

σ_t: Measurement error per treatment arm

$$\sigma_t \sim Unif(0,10); t = 1,2$$

The θ_t parameters represent the multiplicative proportional slowing in rate of progression for treated relative to placebo (*t=1*); also referred to as the functional-impairment progression rate ratio (FPRR). For placebo, the FPRR is assumed to be 1 ($\theta_1 = 1$). Thus, the FPRR parameter for treatment (Lu AF82422) represents the multiplicative change to the mean progression of a placebo patient. If the FPRR is less than 1 then the progression for treatment t is slower than for placebo. A value of FPRR = 0.75 corresponds to a 25% slowing in progression and a value of 0.25 represents a 75% slowing in progression. The errors for the individual observations are modelled as independent normal distributions with a standard deviation of σ.

14.3.2 Posterior Summaries

The Bayesian posterior distributions of all model parameters are calculated using Markov chain Monte Carlo (MCMC). The algorithm allows the generation of at least M = 100,000 draws from the joint posterior distribution for all model parameters. In particular, summaries of the Bayesian posterior distribution for the effect of Lu AF82422 compared to placebo, θ_2, will be provided including the mean, median and 95% credible intervals together with the probability that the active dose is superior to placebo,$\Pr(\theta_2 < 1)$. In addition, the probability of at least a 20% slowing effect will be presented,$\Pr(\theta_2 < 0.8)$, and the probability of at least a 30% slowing effect will be presented,$\Pr(\theta_2 < 0.7)$.

Finally, summaries of the Bayesian posterior distribution for the remaining model parameters will be provided including the mean, median and 95% credible intervals.

14.3.3 Rationale for Selected Analysis Method for the Primary Endpoint

It is believed, that applying the Bayesian progression model is an appropriate and powerful way of analysing MSA disease progression data in this context, since:

- The Bayesian methodology provides relatively simple computational and interpretable posterior probabilities for decision-making. In addition, it offers a robust performance in relation to convergence, as well as consistency across the performed analyses.
- There is a strong indication based on available 12-24 months MSA progression data[1] (i.e., UMSARS total and part I scores) of a steep and nearly linear disease progression trajectory; especially for the earlier patient segment, making it meaningful to talk about a change in the slope or a slowing down of progression.
- Due to the parametrization of effect expressed common across all visits, the model offers an easy interpretable target of estimation being the percentage-wise slowing in progression through up to 72 weeks treatment for Lu active dose compared to placebo.
- Based on the Lu AF82422 hypothesized mechanism of action, an early trend in UMSARS in favor of Lu AF82422 is reasonable due to the expected immediately steep MSA progression curve. Furthermore, the UMSARS is assessed for the first time at Week 12 following multiple dosing allowing time for initial treatment manifestation. Assuming that such an early trend will be further substantiated over time in a proportional-like manner due to the hypothesized moderation of the MSA pathology by Lu AF82422 (i.e., inhibition of seeding of pathological form(s) of alpha-synuclein, inhibition of the C-terminal proteolytic cleavage of alpha-synuclein, and potential immune-mediated clearance of alpha-synuclein/mAb complexes by the active Fc region), it seems less likely that the effect will significantly wear-off within the up to 72 weeks treatment period.
- The progression model is better suited for handling individual differences in treatment duration (i.e., when having differences in treatment duration due to the study design or a notable number of drop-outs/deaths); despite incomplete data (<72 weeks), a slope can still be estimated making full use of all patients. In particular, the long duration of the study (48-72 weeks) makes it more relevant to consider the effect integrated over time instead of the change from baseline for a single chosen timepoint.
- The progression model is well suited for handling also differences between visits due to the study design, where all ongoing patients will be called in for their respective end-of-treatment visit when the last patients randomized has completed 48 weeks of treatment.
- For treatment effect, the prior has been selected uniformly within [0, 2] for the active arms compared to placebo. In this way the prior is centred around no effect, i.e., $\theta_t = 1$, with $\theta_2 < 1$ referring to a slowing in progression, and $\theta_2 > 1$ referring to an increase.
- Remaining priors have been selected in a conservative and basically 'non-informative' manner by using relatively large outcome spaces. For the fixed effects of visit, β_j, a normal distributed prior centred around zero with a variance of 100 has been selected, since between-visit changes in the UMSARS scale can be both positive and negative with a relatively high variability. However, due to the rather aggressive disease progression observed within MSA, it is expected that the cumulated sums of β_j's are positive leading to an interpretation of $\theta_2 < 1$ being an improvement.

- For the subject-level effect a fairly simple parametrization has been selected by assuming these to be random with a uniformly shaped hyper-prior on the standard deviation within [0, 20]. In this way the covariance structure is assumed to be relatively simple.
- Since used for stratification, CCI and study region, respectively, will be accounted for by including as multiplicative fixed covariate effects parametrized on the logarithmic scale. For both parameters, a reference level will be set to zero and for the remaining level(s) a normally distributed prior will be selected centred around zero (for no difference) with a variance of 100. In this way the effect can go in either direction with little restriction on the size.
- The model has shown little bias in the treatment estimate for the selected scenarios. Additionally, under various formulations of the null hypothesis the model has with the chosen thresholds shown to adequately control the type 1 error on an overall 5% significance level evaluated 1-sided and has attractive type II error control under the alternative.
- It is already an established approach within other neurodegenerative diseases (e.g., AD[2,3]) and within diseases that cause progressive weakness and loss of muscle mass (e.g., Duchenne muscular dystrophy[4] or GNE myopathy[5]) to model disease progression and show changes to expected disease deterioration as a change in the slope of progression.

To evaluate the appropriateness of the proposed progression model and the underlying assumptions, a number of sensitivity analyses will be conducted, incl. a MMRM to evaluate consistency across models especially in relation to how effect matures over time. Such approach will also be used to evaluate potential bias in effect estimates. See 14.3.5 Sensitivity Analyses of the Primary Endpoint for further details.

14.3.4 Evaluation of Model Assumptions for the Primary Analysis of the Primary Endpoint

The following goodness-of-fit diagnostics will be performed to assess the goodness-of-fit of the Bayesian primary repeated measures analysis:

- Residual plots for UMSARS TS: residuals vs. fitted values of UMSARS TS at each visit and for each treatment group.
- Mean and SD in change from baseline of UMSARS TS at each 12-week visit for each treatment group compared to model fitted expected values from primary analysis model.

14.3.5 Sensitivity Analyses of the Primary Endpoint

Handling of Missing Data

The following sensitivity analyses will be performed in case of drop-out/withdrawal/death, where the below rules will be applied for the visit following the event for subjects not having

complete data from the Withdrawal Visit, assuming that intermediate missingness will be 'missing at random':

- For withdrawal due to death, impute individual missing UMSARS items as worst possible score in case of death.
- For withdrawal due to other reasons, impute individual missing UMSARS items as worst observed within-subject value for the specific item at any post-IMP time point.
- For withdrawal due to other reasons, impute individual missing UMSARS items as the worst value observed within the combined treatment and control arms at any post-IMP time point.

Two analyses will be performed in both cases using the above strategy to handle withdrawal due death. Following each of the above strategies for handling withdrawals due to other reasons will then be applied.

To explore further the impact of death, a non-parametric joint-rank analysis will be performed to account for informatively missing data by ranking patients based jointly on their Week 48 UMSARS score (UMSARS TS and mUMSARS) and 48-week survival, i.e., time-to-death. Such analysis corresponds to a composite strategy. In case of missing Week 48 data for survivors, Multiple Imputation (MI) will be performed in which the remaining missing data will be imputed corresponding to a missing-at-random assumption.

Missing data for UMSARS Week 12 up to Week 48 will be addressed by using Multiple Imputation. Missing data will be imputed using a sequential regression-based multiple imputation method, based on the imputation models established from the corresponding randomized treatment group. Example SAS code for this imputation can be found in Appendix II.

200 imputed datasets will be created, which will each be analysed and combined as follow.

Define score, u_{ij}, which is chosen to reflect whether patient i has had the more favourable UMSARS score than patient j. In the case where both patient i and j died prior to the Week 48 assessment:

- $u_{ij} = 1$ in the case where patient i died after patient j
- $u_{ij} = -1$ in the case where patient i died before patient j
- $u_{ij} = 0$ in the case where it cannot be determined who died first

In the case where patient i died prior to the Week 48 assessment, and patient j has not died prior to the Week 48 assessment:

- $u_{ij} = -1$

In the case where patient i did not die prior to the Week 48 assessment, and patient j died prior to the Week 48 assessment:

- $u_{ij} = 1$

In the case where both patient i and patient j are alive at Week 48 assessment:

- $u_{ij} = -1$ when UMSARS score for patient i at Week 48 > UMSARS score for patient j at Week 48
- $u_{ij} = 1$ when UMSARS score for patient i at Week 48 < UMSARS score for patient j at Week 48
- $u_{ij} = 0$ when UMSARS score for patient i at Week 48 = UMSARS score for patient j at Week 48

Using the u_{ij} for every pair of patients defined above, a score is assigned to each subject, $U_i = \sum_{i \neq j} u_{ij}$.

A t-test is applied to the U_i scores to compare the treatment groups. The estimated mean difference and associated SE from each of these analyses will be combined using Rubin's Rule. The p-value from this combined analysis will be presented.

Assumptions of Primary Efficacy Model

The following analyses will be conducted to test the sensitivity of the results to the primary efficacy model assumptions:

- The Bayesian repeated measures primary analysis model will be explored for sensitivity to priors by using a sceptical alternative for θ_2, i.e., using a PERT distribution with mode 1.1 and a shape of 7.44 corresponding to a prior that Lu AF82422 is doing 60% worse than placebo.
- The UMSARS TS will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). The model will include the following: region, CCI and treatment (Lu AF82422 and placebo) as fixed factors, baseline UMSARS TS as continuous covariate, treatment-by-week interaction and baseline UMSARS TS-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be performed using all available observations (observed cases [OC] data) in the DBP. The estimated treatment differences between Lu AF82422 and placebo obtained at Week 48 will be estimated based on the least squares means for the treatment-by-week interaction in the MMRM model. Estimated treatment differences at Week 60 and 72 will be exploratory. In case of issues converging, a Toeplitz structure will be fitted instead.
- A constrained longitudinal data analysis with natural cubic splines that treats time as continuous, which allows separate splines for each treatment (Donohue et al, 2023)[6]. The natural cubic spline model assumes:

$$Y_{i,j} = \beta_0 + \sum_{k=1:m}(\beta_k \cdot b_k(t_j)) + Active_i \cdot \sum_{k=1:m}\left(\gamma_k \cdot b_k(t_j)\right) + \varepsilon_{ij},$$

where $b_k(t)$ are the known spline basis functions for a given set of knots and extreme values of t, with Interior knots spaced according to quantiles of *t*. The resulting curve for the placebo group is defined by the natural cubic spline $f(t) = \beta_0 + \sum_{k=1:m}(\beta_k \cdot b_k(t_j))$; while the natural cubic spline $g(t) = \sum_{k=1:m}(\gamma_k \cdot b_k(t_j))$ represents the treatment group difference over time and is constrained to be zero at time zero. Estimation of the unknown parameters (βs and γs) is accomplished with maximum likelihood estimation. It is to be noted, that a special case of the spline parameterization with visit times set to the planned times and knot locations chosen to match the planned visit times is equivalent with a categorical-time mean structure as found in the MMRM.

In this case, a natural spline with one interior knot at the median observation time has been selected as proposed by Donohue et al in their paper. In addition, as covariance matrix an un-structured approach will be applied. The model will in addition be adjusted for MSA sub-type and the two categorical covariates used for stratification, i.e., Region and CCI . The primary evaluation for the spline model will be performed at Week 48 and additional time points will be exploratory.

In fitting the model, the basis for the natural cubic splines is generated using the SAS® code given in the Appendix II.

14.3.6 Subgroup Analyses of the Primary Endpoint

Subgroup analyses of the primary endpoint will be performed using the Bayesian repeated measures primary analysis model for the following subgroups:

- Use of concomitant medication (categorised into PD and autonomic dysfunction medication according to chapter 9). Two analyse will be performed: 1) where concomitant medication was already started up prior to baseline and continued after baseline, and 2) where concomitant medication was initiated or change in dose of existing medication after baseline
- Presence of MRI abnormalities at Screening supporting the diagnosis of MSA (i.e., 'yes' to at least one of the MRI abnormalities according to Screening MRI procedure)
- MSA sub-group (MSA-P and MSA-C)
- Pre-dose MSA positive result in the qualitative alpha-synuclein seeding aggregation assay (SAA), i.e., positive for alphaSyn seed amplification pattern predominantly found in subjects with MSA

14.3.7 Covariate Analyses of the Primary Endpoint

The effect of covariates on the primary endpoint will evaluated applying an ANCOVA to the change from baseline to Week 48 in UMSARS TS including the baseline UMSARS TS, Region, and CCI . The following covariates will be added and evaluated once at a time:

- age (categorized as <50yrs; 50-60; >60yrs)
- gender (female/male)
- race
- time-since-symptom onset (as yearly intervals)

- baseline plasma/CSF alpha-synuclein and CSF NfL (defined as baseline lower/middle/upper tertile)
- baseline disease severity according to category of CGI-S and UMSARS part IV (global disability score 1-5), and SE-ADL (defined as baseline lower/middle/upper tertile)

14.4 Analysis of the Secondary Endpoints

14.4.1 Analysis Methodology for the Key Secondary Endpoint

- For the key secondary endpoint, i.e., the changes in mUMSARS from baseline up to EoTDB, a Bayesian repeated measures model will be applied similar to the primary analysis.

Sensitivity analyses to the key secondary analysis will be set up similar to the sensitivity analyses described for the primary endpoints under section 14.3.5 Sensitivity Analyses of the Primary Endpoint(s).

14.4.2 Analysis Methodology for the Secondary Endpoint

- For the UMSARS Part I, UMSARS Part II and the aUMSARS, a similar Bayesian progression model and estimand strategy to the primary analysis will be applied.
- For remaining continuous secondary endpoints (e.g., clinical scales/assessments and MRI parameters), the change from baseline to EoTDB will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM). The model will include the following: region, CCI and treatment (Lu AF82422 and placebo) as fixed factors, baseline as continuous covariate, treatment-by-week interaction and baseline-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be performed using all available observations (observed cases [OC] data) in the DBP. The estimated treatment differences between Lu AF82422 and placebo obtained at Week 48 will be estimated based on the least squares means for the treatment-by-week interaction in the MMRM model. Estimated treatment differences at Week 60 and 72 will be exploratory. In case of issues converging, a Toeplitz structure will be fitted instead.
- Categorical secondary endpoints will be evaluated using shift-tables evaluated at Week 48.
- Adjusted number of falls per individual per fall diary period in the DBP, according to the patient fall diary, will be analysed applying a MMRM as described above, if appropriate. Cause and consequence of falls will be evaluated descriptively.
- Time-to-wheelchair endpoint as assessed in the physical examination (first time point as ‘full time user’) following up to 72 weeks of treatment will be presented by a Kaplan-Meier plot and analysed applying a Cox proportional-hazards model. The model will be adjusted for stratification factors.
- Lu AF82422 plasma concentrations, CSF concentrations, and the CSF/plasma concentration ratios during treatment for all patients will be presented descriptively. A

population pharmacokinetics analysis (popPK) will also be performed and included in a separate reported.

- Absolute values and changes from baseline to EoTDB in blood and CSF biomarkers will be analysed descriptively (i.e., NfL, t-tau, truncated alpha synuclein). A MMRM will be applied for the changes from baseline to EoTDB. If required, a log transformation will be applied for normalization.
- TE of Lu AF82422 to α-synuclein in plasma and CSF will be presented descriptively as 'free' α-synuclein, 'total' α-synuclein and ratio of 'free' to 'total' α-synuclein. In addition, TE will be plotted vs. concentration of Lu AF82422 to characterize the relationship.
- Results from the semi-quantitative alpha synuclein seeding assay (SAA), i.e., the SD50 – representing the time to reach 50% max, will be presented descriptively over time.
- Gait and balance parameters derived from the sensor based FeetMe® device will primarily be analysed descriptively for the SBS. a MMRM model, like the one described above for continuous secondary and exploratory endpoints, will be applied to the change from baseline. Correlation to the key progression markers, that is the UMSARS scores and MRI parameters, will be explored graphically using scatterplots.

14.5 Additional Analyses of Primary and Secondary Endpoints

A number of additional analyses is planned to evaluate the relationship between the primary and selected secondary/exploratory endpoints:

- Relationships between selected continuous endpoints, i.e. UMSARS total score and subdomains, MRI, blood/CSF NfL, α-synuclein, COMPASS-S/SC, CGI-S, PGI-S, SE-ADL, gait parameters and EQ-5D-5L VAS will be explored using scatterplots for both absolute values and change from baseline.
- The minimal clinically important difference within-patient (MCID) on each scale will be investigated. Further details on the work identifying the MCID will be described in a specific separate *Psychometric SAP*. The outcome of the MCID analysis will be reported in a separate report.

14.6 Analysis of Exploratory Endpoints

For exploratory endpoints the following methodology will be applied:

- For continuous exploratory endpoints, a MMRM will be applied for observed data (OC), using observed data from the Withdrawal Visit for patients dropping out (for other reasons than death), if available. The model will contain the following effects: baseline score, treatment, visit, CCI [redacted], Region, treatment*visit and baseline score*visit as fixed effects and subject as random effect. The main comparison will be at Week 48. Initially, an unstructured covariance matrix will be fitted. In case of issues converging, a Toeplitz structure will be used.
- Time-to-event exploratory endpoints up to EoTDB will be analysed applying a Cox proportional-hazards model.

- Number of falls per individual according to the sensor-based PAMSys device will be analysed descriptively including data from the pre-defined periods only.
- Target engagement and biofluid markers in general will primarily be explored graphically. If applicable, relevant efficacy endpoints will be evaluated especially for patients obtaining target engagement.
- The analysis of Screening and Exit semi-structured, qualitative interviews will be prespecified in a specific Qualitative Analysis Plan (QAP). Whenever a combined quantitative and qualitative approach is considered, a dedicated Mixed Method QAP will be developed.

Open-label extension (OLE)

- All continuous endpoints following treatment extension will primarily be analysed descriptively. In addition, a MMRM will be applied similar to the one described above to the change from the original baseline (DB baseline), where patients originally treated with pbo will be kept as a separate group. No formal testing will be applied.

15 Testing Strategy

15.1 Calibrating primary analysis

The final analysis will use all available data on all enrolled participants at baseline through 48-72 weeks. A success threshold is defined for the final analysis to maintain an overall alpha of 5% evaluated one-sided. The effect of Lu AF82422 will be evaluated using a Bayesian posterior probability of superiority relative to placebo with a threshold of 97.5% identified through simulations.

Lu AF82422, CCI dose: $\Pr(\theta_2 < 1) > .975;$

15.2 Testing Strategy including Secondary Endpoint(s)

To protect the type I error for the primary analysis, i.e., analysis of UMSARS TS and the key secondary analysis, i.e., analysis of mUMSARS, both using the Bayesian progression model, a testing strategy will be applied. Firstly, both endpoints will be evaluated individually by applying the pre-defined threshold to the posterior probability for Lu AF82422 being superior to placebo, where the thresholds have been calibrated to be equivalent to the targeted 5% significance level evaluated one-sided. Following, the Fixed-Sequence Method will be applied evaluating the two prioritized analyses in a hierarchical manner:

- Step 1: UMSARS TS evaluated using the derived posterior probability (test equivalent to a one-sided 5% level). If significant,
- Step 2: mUMSARS evaluated using the derived posterior probability (test equivalent to a one-sided 5% level).

16 Safety

16.1 Adverse Events

16.1.1 General Methodology for Adverse Events

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

Tables by preferred term and tables by system organ class (SOC) and preferred term (PT) will be sorted in descending order based on the percentages of patients with these adverse events.

Unless otherwise specified, the summaries of adverse events will include the number and percentage of patients with an adverse event, and the total number of events.

In summaries of TEAEs by preferred term and intensity, and in summaries of causally related TEAEs by preferred term and intensity, the maximum intensity for the preferred term within an analysis phase will be used.

Listings of adverse events will be sorted by site, patient number, and adverse event start date, and will include preferred term, investigator term, adverse event start date, end date,, duration of the adverse event, date of death, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included.

16.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 26.0 or later.

16.1.3 Classification of Adverse Events

Adverse events will be classified according to the date of onset (or worsening of intensity/seriousness) of the adverse event and end date as follows:

- *pre-treatment adverse event* – an adverse event that starts (or worsens) on or after the date the patient signed the *Informed Consent Form* and prior to the date and time of first dose of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts (or worsens) on or after the date of first dose of IMP

An adverse event is considered causally related to the use of the IMP when the causality assessment by the investigator is probable or possible.

Data handling of change in intensity or seriousness of adverse events is described in section 24.5.2.

16.1.4 Allocation of TEAEs to Study Periods

TEAEs will be assigned to periods according the following:

- *Adverse events in the double-blind period (DBP)* – all TEAEs with date of onset or worsening of intensity/seriousness after first dose of IMP in the DBP and until first dose of IMP in the OLE period (planned for Visit 1E – for patients entering the OLE) or the Safety Follow up visit for the DBP (SFU Visit 25 – for patients NOT entering the OLE) (assigned APHASE = DOUBLE BLIND).
- *Adverse events in the Open-Label Extension period* – TEAEs with date of onset or worsening of intensity/seriousness after first dose of IMP in the OLE period (Visit 1E) and until the final Safety Follow up visit for the OLE (Visit 64E) (assigned APHASE = OLE).

The above imply that an adverse event, with multiple levels of intensity/seriousness, may be reported for more than one phase but only if it worsens. For instance, an adverse event ongoing at the end of the End-of-Treatment (EoT) visit which worsens after the first dosing in the OLEP, will be reported both for the double-blind period (DBP) and for the open-label period, but an adverse event ongoing at the EoT visit, which reduces in intensity/severity will only be reported in the DBP.

16.1.5 Presentation of Adverse Events

All adverse events will be listed for the APRS.

An overview of the PYE and number and percentage of patients with TEAEs, serious adverse events (SAEs), or adverse events leading to withdrawal, and of patients who died will be provided based on the APTS for the open-label and safety follow-up period.

For TEAEs, SAEs, and adverse events leading to withdrawal/death, the total number of events will be included.

16.1.6 Presentation of Treatment-emergent Adverse Events

For TEAE's, the following summaries will be provided by study period (DBP, OLEP and the safety follow-up periods, if appropriate) for the APTS:

- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs with an incidence ≥ 5% by preferred term
- TEAEs by causality (possible, probable, not related), SOC and preferred term
- TEAEs by intensity (*mild*/*moderate*/*severe*), SOC, and preferred term

The summaries will be provided for the APTS for the study periods.

For TEAEs occurring on the day of dosing after infusion start, TEAEs with missing start times will also be included.

16.1.7 Presentation of Deaths

All the adverse events in patients who died will be listed for the APRS.

16.1.8 Presentation of Serious Adverse Events

All the SAEs will be listed for APRS by study period.

Treatment-emergent SAEs for the APTS will be summarized by:
- SOC and preferred term
- preferred term

16.1.9 Presentation of Adverse Events Leading to Withdrawal

All the adverse events leading to withdrawal will be listed for the APRS.

TEAEs leading to withdrawal will be summarized by:
- SOC and preferred term
- preferred term

16.1.10 Presentation of Adverse Events Leading to Study Drug Infusion Interruption or Infusion Rate Reduction

All AEs leading to study drug infusion interruption or infusion rate reduction will be listed for the APRS.

TEAEs leading to study drug infusion interruption or infusion rate reduction will be summarized based on APTS by:
- SOC and preferred term
- preferred term

16.1.11 Presentation of Adverse Events requiring additional data collection

Treatment-emergent adverse events related to Type I, II and III Hypersensitivity reactions have been defined as study-specific AE's requiring additional data collection. Events considered Hypersensitivity reactions by the Investigator will be collected during the study using a dedicated Hypersensitivity Form.

Summaries will be provided for each period for the APTS for Hypersensitivity Reactions (as reported by the investigator) and for each of the following sponsor defined categories (see Appendix VI).
- TEAEs with a PT within the SMQ of Hypersensitivity (narrow scope)
- TEAEs with a PT 'Cytokine release syndrome'
- TEAEs with a PT within the SMQ Vasculitis (narrow scope) or any of the 15 defined single PTs

Hypersensitivity reactions will be listed by category by the APRS.

16.2 General Methodology for Other safety Data

Unless otherwise specified, tables, graphs, and listings will be based on the APTS.

All tables and graphs will be presented by treatment group.

The denominators for the summaries of a given variable will be based on the number of patients with non-missing values at a given visit or during the assessment period.

Descriptive statistics for the safety variables, both absolute values and changes from baseline, will be presented by visit, separately for each period.

The number and percentage of patients with at least one PCS value at any post-baseline assessment time point will be summarized by variable, separately for each period. All available assessments in each period will be included in the evaluation of PCS values.

For patients with post-baseline PCS values, listings will be provided including all the values for those patients for the variable, with flagging of PCS values and out-of-reference-range values.

For vital signs being measures multiple time during a visit values will be presented graphically within visit over time, where the position will be indicated.

All the adverse events in patients with post-baseline PCS values will be listed by treatment group and patient screening number; the listing will include the PCS value, the assessment date, the change from baseline in PCS value, the preferred term for the adverse event, and start date and stop date of the adverse event. The PCS values and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event

16.3 Clinical Safety Laboratory Test Data

16.3.1 Data Presentation

The PCS criteria used for the clinical safety laboratory tests can be found in Appendix V.

The clinical safety laboratory test values will be presented both in conventional and Système International (SI) units.

16.4 Vital Signs and Weight

The PCS criteria used for vital signs and weight are the Lundbeck standard PCS criteria described in SOP_09978: *GPV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 4.

16.5 ECG

The PCS criteria used for the ECG parameters are the Lundbeck standard PCS criteria described in SOP_09978: *GPV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 5.

In addition to the tables and listings specified in section 16.2, absolute values and changes from Baseline in QTcF will also be summarized categorically by visit and treatment. The categories that will be used are as follows for the absolute QTcF values:

- QTcF interval < 450 msec
- QTcF interval 450 - 480 msec
- QTcF interval > 480 - 500 msec
- QTcF interval > 500 msec

The categories that will be used for the change from baseline QTcF values are:

- QTcF interval increase from baseline > 30 msec
- QTcF interval increase from baseline > 60 msec

Furthermore, the number and percentage of patients being classified as having either a normal, abnormal but not clinically significant, abnormal and clinically significant, or not interpretable ECG result based on the overall interpretation of the ECG from the investigator will be summarized by visit and treatment group.

16.6 Columbia-Suicide Severity Rating Scale (C-SSRS) Scores

The C-SSRS was administered:

- for Screening at Visit 1: The C-SSRS assessment that collects a lifetime and 6 months recall (using the *Baseline*/*Screening Version*)
- for Baseline at Visit 3: The C-SSRS assessment that collects a lifetime and 6 months recall (using the *Baseline*/*Screening Version*)
- For subsequent visits: The C-SSRS assessment that collects information since the previous visit (using the *Since Last Visit Version*)

The numbers and percentages of patients with lifetime, 6 months pre-baseline or post-baseline suicide-related events based on the C-SSRS will be summarized by treatment group. For each summary, the most severe item with an answer "Yes" for each patient according to the ordering given in Panel 3 is displayed. For the post-baseline assessments, the summaries will be by treatment group and the most severe item with an answer "Yes" for the whole period for each patient related to suicidal ideation and/or behaviour will be summarized.

The number and percentage of patients with *no suicidal ideation or behaviour* will be included in the summaries.

Panel 3 C-SSRS Scores

C-SSRS Score		Related to:
1	Wish to be dead	Suicidal ideation
2	Non-specific active suicidal thoughts	
3	Active suicidal ideation with any methods (not plan) without intent to act	
4	Active suicidal ideation with some intent to act, without specific plan	
5	Active suicidal ideation with specific plan and intent	
6	Preparatory acts or behaviour	Suicidal behaviour
7	Aborted attempt	
8	Interrupted attempt	
9	Non-fatal suicide attempt	
10	Completed suicide (only applicable for the post-baseline assessments)	

The C-SSRS scores will be summarized based on the APTS.

Missing C-SSRS scores will not be imputed.

Positive responses to *non-suicidal self-injurious behaviour* will be summarized separately.

For patients with any post-baseline suicidal ideation or behaviour (C-SSRS scores of 1 to 10), listings will be provided based on APRS including all C-SSRS scores for those patients

16.7 MRI Safety Findings

MRI safety findings will be listed.

16.8 Pregnancy Test

Pregnancy test results will be listed for patients with any positive results.

16.9 Events of Death

Events of deaths will be summarized by treatment group, reason of death and study period . In addition, events of death will be listed.

Time-to-death will be investigated graphically using a Kaplan Meier plot and modelled, if applicable, by applying a Cox proportional-hazards model incl. treatment group, CCI and region as covariates. For patients with no unique date-of-death the date of the last completed visit will be used. Patients still alive at the time of the safety follow-up visit will be censored using the date of the last safety follow-up visit as last observed time point.

17 Pharmacokinetic/Pharmacodynamic Analysis

The population pharmacokinetics of Lu AF82422 will be determined by means of non-linear mixed effect analysis. Estimated parameters of plasma exposure per patient (e.g. AUC and Cav) will be related to the efficacy and safety/tolerability in an exploratory PK/PD analysis. Details of the popPK and PK/PD analyses will be given in a separate popPK/PD analysis plan. The results of the popPK and PK/PD analyses will be reported in a popPK/PD report and relevant parts of it might be given in the clinical study report.

18 Immunogenicity Analysis (ADA)

The analysis of anti-Lu AF82422 antibodies will be performed for all subjects in the APTS receiving at least one dose of Lu AF82422. Subjects receiving placebo will not be analyzed for anti-Lu AF82422 antibodies.

Panel 4 ADA definitions

Pre-existing ADA	Refers to antibodies reactive with the biologic drug that are present in subjects before drug administration
Treatment-induced ADA	ADA developed de novo following drug administration
Treatment-boosted ADA	Pre-existing ADA that were boosted to a higher-level following drug administration, i.e., titer is greater than the baseline titer by a fourfold increase
Neutralizing ADA (NAb)	ADA that inhibits or reduces the pharmacological activity of the drug
ADA-positive subject	A subject with at least one treatment-induced or treatment-boosted ADA-positive sample at any time during the treatment or follow-up observation period
ADA-negative subject	A subject without a treatment-induced or treatment-boosted ADA-positive sample during the treatment or follow-up observation period
ADA-inconclusive subject	A subject who cannot irrefutably be classified as ADA-negative since drug is present in the same sample at a level exceeding the validated drug tolerance level, i.e., drug tolerance
Transient ADA	ADA detected only at one sampling time point during the treatment or follow-up observation period, or ADA detected at two or more sampling time points during the treatment separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative
Persistent ADA	Treatment-induced ADA detected at two or more sampling time points during the treatment (including safety follow-up period) where the first and last ADA-positive samples are separated by a period of 16 weeks or longer, or ADA incidence only in the last sampling time point of the treatment study period or at a sampling time point with less than 16 weeks before an ADA-negative last sample
Onset of ADA	Onset defined as the time period between the initial administration of IMP and the first instance of treatment-induced ADA
Duration of ADA	Referring to the longevity of treatment-induced ADA
ADA prevalence	The proportion of subjects having anti-drug antibodies (including pre-existing antibodies) at any point in time
ADA incidence	The proportion of subjects found to have seroconverted or boosted their pre-existing ADA during the study period

The following analysis will be carried out to the extent meaningful based on the total number of subjects identified with pre-existing or treatment-induced ADA.

If appropriate, data will be provided for:

- Pre-existing antibodies: ADA-positive subjects as a percentage of the total number of subjects, titer range (median and interquartile range (IQR)), percentage of treatment-boosted ADA-positive subjects, and duration of only pre-ADA, i.e., pre-ADA remained of same titer during the duration of study.
- Overall ADA prevalence: the number of ever-ADA-positive subject as portion of all study participants.
- Overall ADA incidence: combined results of treatment-boosted ADA-positive subjects and treatment-induced ADA-positive subjects (i.e., ADA-negative at baseline). For treatment-induced ADA incidence, peak positive titer and range (median, IQR). For treatment-boosted ADA, incl. the computed fold increase in titer (ratio of peak post-administration titer to baseline titer) and range of titer increases (median, IQR).
- Onset and duration of treatment-induced ADA. Regarding duration, a differentiation will be made between transient and persistent treatment-induced and boosted ADA.

Furthermore, the potential impact of ADA on PK, PD (as assessed by target engagement (TE)), clinical safety and efficacy will be explored descriptively for subjects with pre-existing or treatment-induced ADA.

- PK and PD: will be evaluated stepwise firstly looking into mean exposure for ADA-positive vs. ADA-negative. In case any notable difference is found, PK will be considered by categorizing subjects into patients with impact of ADA vs. patients with no impact of ADA based on individual exposure over time to identify potential neutralizing/clearing ADA. To explore the ADA impact on PD, Safety and Efficacy the following analyses will be performed for ADA-positive vs. ADA-negative. Whether ADA is evaluated to have impact or not for an individual patients will be documented in patient listing.
- PD: TE as assessed by the plasma ratio of ‘free’ alpha-synuclein over ‘total’ alpha synuclein, plasma NfL, and MRI volumetric (as assessed by changes in primary regions)
- Safety: The number of hypersensitivity relevant TEAE’s presented by SOC and PT, with focus on nature and timing of TEAE’s (see below)
- Efficacy: Changes-from-baseline in UMSARS TS.

Nature of TEAEs

Consequences of immunogenicity on safety include the following TEAEs:

- Hypersensitivity reactions (as reported by Investigator)
- Hypersensitivity related TEAEs as Type I, II and III jointly, i.e., with a PT within 1) the SMQ of Hypersensitivity (narrow scope), 2) ‘Cytokine release syndrome’, and 3) the SMQ Vasculitis (narrow scope) or any of the 15 defined single PTs (see Appendix VI)

Timing of the TEAE

TEAE is only potentially related to immunogenicity if there is a temporal relationship to the ADA response, i.e., if there is a temporal relation between the onset of the TEAE and participants being or turning ADA positive, i.e., the participant is 'TEAE coincident ADA positive'.

All immunogenicity data will be listed by subject and period.

19 Blinded Data Reviews

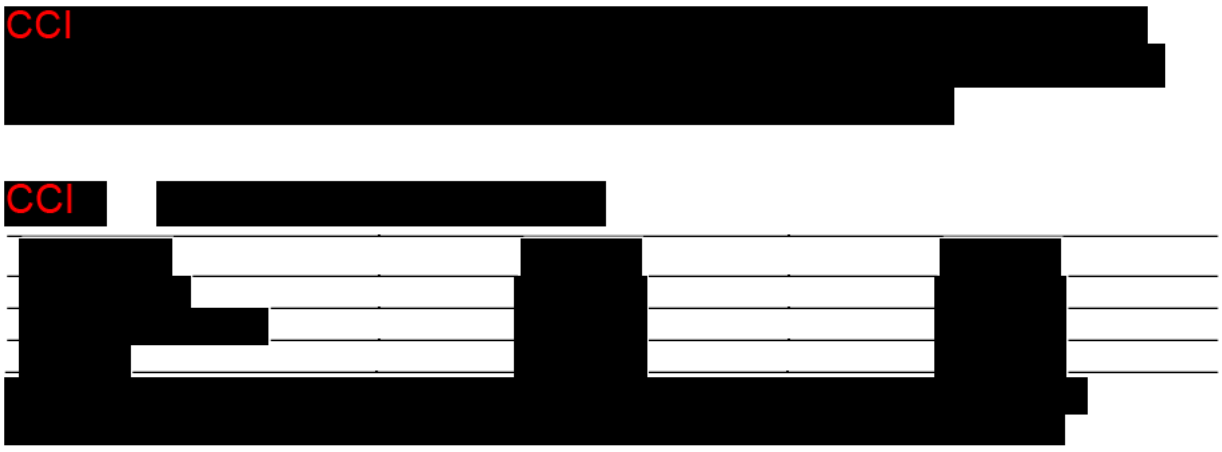
A blinded data review will take place throughout the study to ongoing handle data issues. The reviews may include, but are not limited to, data quality, protocol adherence, and the appropriateness of design assumptions.

An independent Safety Data Monitoring Committee (DMC) will regularly monitor the patients' safety data according to the DMC Charter. The DMC will have access to unblinded information for the double-blind treatment for each patient. Members of the DMC will not be involved in other study-related tasks.

20 Interim Analyses

No interim analyses will be conducted for this study.

21 Sample Size Considerations



The 18331A sample size has been selected to ensure an appropriate power to detect a 40% slowing in MSA progression in the Lu AF82422 CCI dose group compared to the placebo group on a 5% significance level evaluated 1-sided. Applying a repeated measures model with proportional treatment effect, yields an approximate 75% power when having N=60 patients allocated 2:1 in favour of Lu AF82422 treatment (i.e., 40 on Lu AF82422 *versus* 20 on

placebo) when using the NLMIXED procedure for simulating in SAS®. To account for differences in treatment duration due to the study design, approximately 50% of the patients are expected to contribute with 60 weeks data and 25% of the patients with full 72 weeks data. On top, an overall 20% drop-out rate has been accounted for. For comparison, it is expected that the frequentist repeated measures model used for simulation is quite similar in relation to performance to the primary Bayesian repeated measures model.

22 Statistical Software

The statistical software used will be SAS®, version 9.4 or later, and R, version 3.12 or later, respectively. For R, the packages Jags and Coda would be required to run the MCMC procedures.

23 Changes to Analyses Specified in the Protocol

- According to SAP section 16.1.4, TEAEs will be assigned to two periods rather than four periods as described in Protocol section 16.10.1, the reason being that the safety follow up periods following the DBP and the OLEP, respectively, will be part of the reporting periods rather than individual periods. In this way the first safety follow up period following the DBP will be reported as part of the DBP, and the safety follow up period following the OLEP will be reported as part of the OLEP.

24 Details on Data Handling

24.1 Derived Variables

Total scores which are (also) calculated by the investigator (e.g. the UMSARS part I score used for inclusion/exclusion), will be represented in two variables: one calculated directly from item scores (e.g. PARAMCD: UMSARSP1) and one with the same name and the extension 'I' containing the total score as calculated by the investigator (e.g. PARAMCD: UMSARSP1I).

24.1.1 Missing Item Scores

Since all rating scales will be performed electronically missing single items should in principle not occur. However, if >20% of the items for a rating scale or subscale are missing, the total score or subdomain score will be set to missing. The maximum number of missing items is given for each in Panel 6.

If number of missing items in a scale does not exceed the maximum number, total scores and/or subdomain scores will be imputed for the UMSARS part I and part II, SE-ADL, and EQ-5D-5L. The general rule when imputing total scores or subdomain scores is that the score will be calculated using the SAS function ROUND:

ROUND ([(sum of scores in non-missing items) / (number of non-missing items) * (total number of items)])

Derived scores including imputed items will be marked (DTYPE = 'EXTRAP').

Panel 6 Maximum Number of Missing Items on Rating Scales

PARAMCD	Description	Maximum Number of Missing Items
UMSARSP1	UMSARS part I score, 12 items	2
UMSARSP2	UMSARS part II score, 14 items	2
EQ5D5L	EuroQoL 5-dimension, 5 items	1

An exception to this rule will be for patients dropping out due to death. In case of death, the total or domain score will be set to worst rank according to Panel 7 below at the visit following the date of death applying both a narrow and a broad visit windowing approach. Hereafter, scores will be set to missing.

In case of drop-out due to death, derived scores will be included for the imputed values marked with D_TYPE = 'WC'.

Panel 7 Imputation of worst rank following events of death

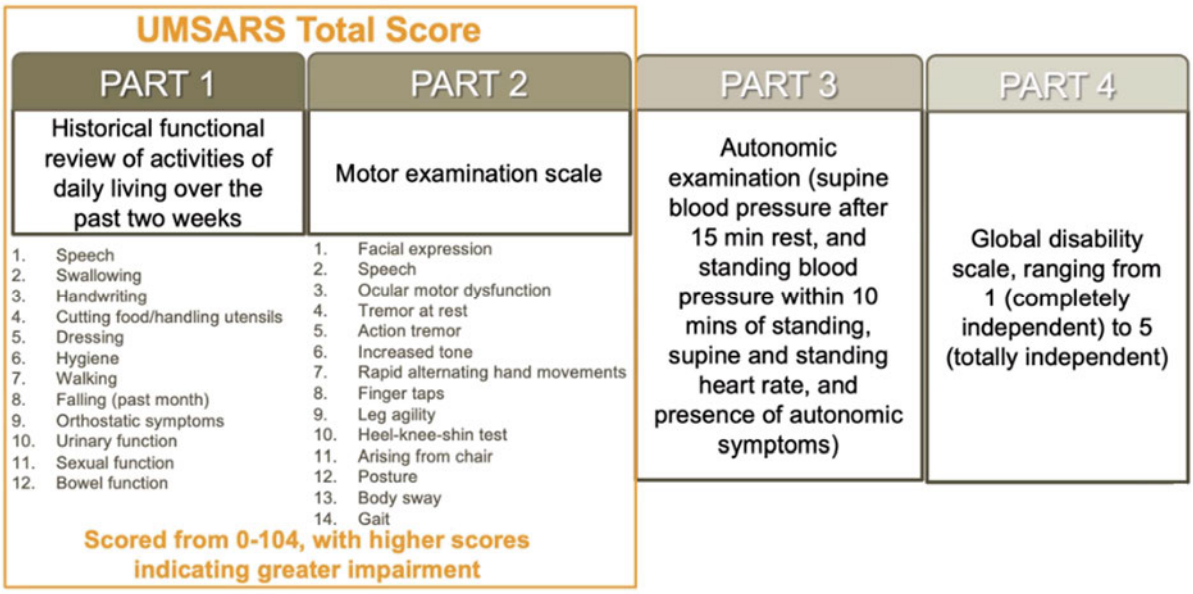
PARAMCD	Description	Imputed worst rank
UMSARSP1	UMSARS part I score	48
UMSARSP2	UMSARS part II score	56
UMSARSTS	UMSARS total score	104
mUMSARS	Modified UMSARS part I score	48
COMPS	COMPASS Select Change - Orthostatic Intolerance Score	*-60*
COMPS	COMPASS Select Change – Secretomotor Score	*-25*
COMPS	COMPASS Select Change – Bladder Score	*-30*
COMPS	COMPASS Select Change – Vasomotor Score	*-10*
COMPS	COMPASS Select Change – Sleep Score	*-25*
SEADL	Schwab & England ADL score	0%
CGIS	Clinical Global Impression score – Severity	4
PGIS	Patient Global Impression score – Severity	4
OGIS	Observer-reported Global Impression – Severity	4
EQ5D5L	EuroQoL 5-dimension, each single domain	5

24.1.2 UMSARS scale

The UMSARS scale consists of four part, i.e. part I-IV, where part I and part II are covering multiple domains with an associated score, whereas part III is covering an autonomic examination and part IV is a 1-dimensional disability scale. In addition, two moderated

UMSARS scores will be derived, i.e., a modified UMSARS part I (mUMSARS) score and an abbreviated UMSARS (aUMSARS) score, respectively.

Panel 8 UMSARS Scale Overview



UMSARS part I and mUMSARS

The UMSARS part I comprises 12 items rating the average functional situation for the past 2 weeks (unless specified) according to the patient and caregiver interview. It covers the following domains: speech, swallowing, handwriting, cutting food and handling utensils, dressing, hygiene, walking, falling, orthostatic symptoms, urinary function, sexual function, and bowel function; all rated 0 to 4, with 0 = not affected/normal; 1= mildly affected/ impaired; 2= moderately affected/impaired; 3= severely affected/impaired; and 4 = helpless or entirely affected/impaired. The UMSARS part I total score ranges from 0 to 48.

If more than 2 items for the UMSARS part I are missing, the score will be set to missing. If no more than 2 items are missing, the score will be equal to the mean of the recorded items multiplied by the total number of items and then rounded to the first decimal place using the SAS function ROUND:

*ROUND ([(sum of scores in non-missing items) / (number of non-missing items) * (total number of items)]).*

The modified UMSARS part I (mUMSARS) score is derived by collapsing the response option 0 and 1 within each item {0 & 1 =1}. Hence, the mUMSARS score ranges from 12 to 48. In case of missing items the same above rule will be applied using the ROUND function.

UMSARS part II

The UMSARS part II comprises 14 items rating different aspects of motor performance for the worst affected limb at the actual visit. It covers the following domains: Facial expression, speech, ocular motor dysfunction, tremor at rest, action tremor, increased tone, rapid alternating movements of hands, finger taps, leg agility, heel-knee-shin test, arising from chair, posture, body sway, gait; all rated 0 to 4, with 0 = not affected/normal; 1= mildly affected/ impaired; 2= moderately affected/impaired; 3= severely affected/impaired; and 4 = helpless or entirely affected/impaired. The UMSARS part II total score ranges from 0 to 56.

If more than 2 items for the UMSARS part II are missing, the score will be set to missing. If no more than 2 items are missing, the score will be equal to the mean of the recorded items multiplied by the total number of items and then rounded to the first decimal place using the SAS function ROUND:

*ROUND ([(sum of scores in non-missing items) / (number of non-missing items) * (total number of items)]).*

UMSARS part III

The UMSARS part III comprises an autonomic examination of systolic blood pressure, diastolic blood pressure, heart rate, and orthostatic symptoms. Supine blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing. Orthostatic symptoms are assessed as 'yes'/'no' and may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, neck and "coat-hanger" ache. The UMSARS part III is not reported as a joint score.

Missing data from UMSARS part III will not be imputed.

UMSARS part IV

The UMSARS part IV comprises a global disability scale ranging from 1-5, with 1='Completely independent. Able to do all chores with minimal difficulty or impairment. Essentially normal. Unaware of any difficulty'; 2='Not completely independent. Needs help with some chores'; 3='More dependent. Help with half of chores. Spends a large part of the day with chores'; 4='Very dependent. Now and then does a few chores alone or begins alone. Much help needed'; and 5='Totally dependent and helpless. Bedridden'.

Missing data from UMSARS part IV will not be imputed.

The UMSARS TS is derived as the sum of part I and part II, hence ranging from 0 to 104. The UMSARS TS will be missing in case either part I or part II would be missing at the same visit.

The UMSARS subscale scores are described in Panel 9.

Panel 9 Derivation of UMSARS total score and domain scores

UMSARS total score and domain scores	Derivation	Range
UMSARS part I	Sum of part I items (1.1-1.12)	0-48
UMSARS part II	Sum of part items (2.1-2.14)	0-56
UMSARS part III	Individual part III items (3.1-3.4)	NA
UMSARS part IV	One item score 4.1	1-5
UMSARS TS	Sum of part I and part II	0-104
Modified UMSARS (mUMSARS)	Sum of part I items with response option 0 and 1 collapsed (=1)	12-48
Abbreviated UMSARS (aUMSARS)	Sum of part I and part II selected items	0-40

* since the abbreviated UMSARS is still under development the final items will be amended at a later point.

24.1.3 Composite Autonomic Symptom Score Select (COMPASS Select)

The COMPASS 31 is a refined, internally consistent, and markedly abbreviated quantitative measure of autonomic symptoms. It provides clinically relevant scores of autonomic symptom severity based on the well-established 169-item Autonomic Symptom Profile (ASP) and its validated 84-question scoring instrument, the Composite Autonomic Symptom Score (COMPASS). However, it applies a much-simplified scoring algorithm, and is suitable for widespread use in autonomic research and practice. COMPASS Select is a simplified version of the COMPASS 31 with selected items only.

Two versions of the COMPASS Select will be applied. At baseline, the COMPASS Select which is a 36-item questionnaire asking into autonomic symptoms within the past year. At subsequent visits, the COMPASS Select Change which is a 16-item questionnaire asking into changes in symptoms since last evaluation.

Since the COMPASS Select Change is licenced by the Mayo Clinic, they will be responsible for deriving the total scores to be used for further analysis. Patient-level single item data and the derived score will be included in sdtm format.

Panel 10 COMPASS Select Change domain scores

COMPASS Change Select Domain*	Questions in domain	Range**
Orthostatic Intolerance domain Score (OI_domain)	Q1, 2, 3, 4, 5, 6	-60-60
Secretomotor domain score (Secretomotor_domain)	Q10, 11, 12	-25-25
Bladder domain score (Bladder_domain)	Q7, 8, 9	-30-30
Vasomotor domain score (Vasomotor_domain)	Q13	-10-10
Sleep domain score (Sleep_domain)	Q14, 15, 16	-25-25
COMPASS Change Select score (COMPASS_Change_Select)	Sum of all 5 domains	-150-150

* COMPASS Select Change domain scores will be derived by Mayo Clinic
** the lower score the more severe symptoms

24.1.4 Schwab & England Activity Daily Living Scale (SE-ADL)

The Schwab and England Activities of Daily Living (SE-ADL) scale is a method of assessing the capabilities of people suffering from impaired mobility. Originally presented at a Parkinson's disease conference, the scale assesses the difficulties patients have completing daily activities or chores. The scale uses percentages to represent how much effort and dependence on others, patients need to complete daily chores. The rating may be given by a professional or by the person being tested. Only the clinician reported part will be included in this study.

Panel 11 SE-ADL Scoring

Percentage of independence	Degree of independence	Description
100%	Completely independent	Able to do all chores without slowness, difficulty or impairment.
90%	Completely independent	Able to do all chores, but with some degree of slowness, difficulty and/or impairment. One might take two times longer than normal to complete chores.
80%	Usually completely independent	Takes two times longer than normal to complete chores.
70%	Mostly independent	Faces more difficulty with some chores. One spends a large part of the day with chores and might take three to four times longer than normal.
60%	Somewhat independent	Can do most chores, but exceedingly slowly and with much effort. Errors are possible during the chores.
50%	Mostly dependent	Needs help with half of every chore. Everything is difficult to one.
40%	Very dependent	Can assist with chores and can complete some alone.

Percentage of independence	Degree of independence	Description
30%	Very dependent	With help, can start chores. One can also complete few chores with effort and help.
20%	Very dependent	Can slightly help with chores but cannot complete any alone.
10%	Fully dependent	Is helpless and somewhat comatose.
0%	Fully dependent	Is bedridden and helpless. One is almost completely comatose.

24.1.5 Clinical Global Impression Severity Scale (CGI-S)

The CGI-S is administered by an experienced neurologist familiar with MSA patients to make an expert clinical global judgement about the severity of the disease across various time points. The neurologist makes a judgement about the total picture of the patient at each visit: the disease severity, the patient's level of distress and other aspects of impairment, and the impact of disease on functioning. The rating is based upon observed and reported symptoms, behaviour, and function in the past seven days. Symptoms and behaviour may fluctuate over a week; the score should therefore reflect the average severity level across the seven days. The CGI-S is rated on a scale ranging from 0 to 4 (whereas the 0 = normal, not impaired; 1 = mildly impaired; 2 = moderately impaired; 3 = severely impaired; 4 = extremely impaired).

24.1.6 Patient global Impression Scale (PGI-S)

The PGI-S is a self-reported single item to evaluate all aspects of patients' MSA symptoms. Patients are asked to choose the response that best describes the severity of their MSA symptoms over the past week. The question is rated on a 5-point scale ranging from 0 to 4 (0 = none; 1 = minor; 2 = moderate; 3 = severe; 4 = very severe). It takes approximately 1 minute to complete the PGI-S.

24.1.7 Observer-reported Global Impression – Severity of Illness (OGI-S)

The OGI-S is a single-question carer/observer-reported outcome to evaluate all aspects of patients' MSA symptoms. Carer/observers are asked to choose the response that best describes the observed severity of MSA symptoms in the person they care for over the past week. The question is rated on a 5-point scale ranging from 0 to 4 (0 = none; 1 = minor; 2 = moderate; 3 = severe; 4 = very severe). It takes approximately 1 minute to complete the OGI-S.

24.1.8 EuroQoL five-dimensional five-levels Scale (EQ-5D-5L)

The EQ-5D instrument comprises a short descriptive system questionnaire and a visual analogue scale (EQ VAS) that are cognitively undemanding, taking only a few minutes to complete. The questionnaire provides a simple descriptive profile of a respondent’s health state. The EQ VAS provides an alternative way to elicit an individual’s rating of their own overall current health. When the descriptive system profile is linked to a ‘value set’, a single

summary index value for health status is derived that can be used in economic evaluations of healthcare interventions.

The EQ-5D-5L covers five domains (i.e. MOBILITY, SELF-CARE, USUAL ACTIVITIES, PAIN / DISCOMFORT and ANXIETY / DEPRESSION) all evaluated using 5 response levels: 'having no problems', 'having slight problems', 'having moderate problems', 'having severe problems' and 'being unable to do/having extreme problems'.

Responses are coded as single-digit numbers expressing the severity level selected in each dimension. For instance, 'slight problems' (e.g. 'I have slight problems in walking about') is always coded as '2'. The digits for the five dimensions can be combined in a 5-digit code that describes the respondent's health state; for instance, 21111 means slight problems in the mobility dimension and no problems in any of the other dimensions. An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111).

The EQ VAS records the respondent's overall current health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

24.1.9 FeetMe® gait parameters

The FeetMe® Monitor sole combines pressure sensors, inertial control units and on-board computing capacity for real-time measurement of walking parameters and plantar pressures, which will be applied periodically for a subgroup according to study procedure (See Appendix IV). The patients receive insoles during scheduled visits and are asked to wear the insoles continuously for 10 days in their home environment in the 5 pre-defined periods (baseline and 4 post-dose assessments).

Equipped with inertial units and plantar pressure sensors, the soles provide quantitative and real time readings of the following gait parameters: heel attack, heel lift, swing duration and duration, single and double support, oscillation time, distance and walking speed, cadence, plantar pressure peak map. These parameters are measured on both feet and thus provide the asymmetries relative to these parameters.

Individual parameters of gait will be derived by-step for each home-based assessment period. For analysis purpose, parameters will be further collapsed using both the median and the 95th percentiles for each day and period, respectively. Additional percentiles will be derived for exploratory purposes. Panel 12 below contains a list of available parameters and endpoint description.

Panel 12 Derivation of gait parameters, by-step

Technology	Parameter	Unit	Endpoint Description
FeetMe® insoles	Gait velocity	m/s	- The median and the 95th percentiles for all gait parameters will be derived for each subject and home-based period - For exploratory purpose, the 95th, the 75th and the 50th percentiles (median) will be derived on an hourly basis for all home-based gait parameters
	Stride length	m	
	Stride duration	s	
	Swing duration	s	
	Stance duration	s	
	Cadence	steps/min	
	Distance travelled per hour	m	
FeetMe parameters calculated at each stride: strideLength (m), widthMotion (m), timeHeelStrike1 (ms), timeHeelStrike2 (ms), timeToeOff (ms), strideDuration (ms), velocity (m/s), cadence (stride/min), swingDuration (ms), stanceDuration (ms), swingPercentage (%), stancePercentage (%), stepTime (ms), stepLength (m), asymmetryParamStepTime (ms), asymmetryParamStepLength (m), singleSupportDuration (ms), doubleSupportDuration (ms), singleSupportPercentage (%), doubleSupportPercentage (%), asymmetryParamStrideDuration (ms), asymmetryParamStrideLength (m), asymmetryParamSingleSupportPercentage (%), strideElevation(cm), Capacitive measures of the 18 pressure sensors (in atmel unity), Centers of pressure (in cm, to confirm)			

In case of large amount of missing data for a subject within a given period consisting of 10 days, the percentiles will not be derived and hence these will be set to missing. Data cleaning, population classification and confirmation of decision rules for derivation of percentiles will take place prior to database lock and will be documented as part of the classification meeting.

Additionally, raw data will be made available as sdtm format.

24.1.10 BioSensics™ PAMSys sensor

PAMSys (Physical activity and posture) is a clinical-grade wearable sensor for continuous remote monitoring of physical activity, sleep, posture, gait parameters and falls, which will be applied periodically for a subgroup according to study procedure (See Appendix IV).

Panel 13 below contains a list of available parameters and endpoint description.

Panel 13 Derivation of PAMSys parameters

Posture and postural transition	Gait parameters
- Posture classification (sitting, standing, walking and lying down) - Postural transition (duration and number of occurrence) - Sedentary behavior	- Number of steps (for example per hour) - Walking duration (for example per hour) - Time stamp of individual steps - Cadence - Cadence variability - Number of episodes of walking (for example per day) - Number of steps per walking episode
Sleep and sleep quality	**Falls and fall risk**
- Start- and end-time of periods of lying down - Sleep onset latency (i.e., time lying down before sleep onset) - Wake time after sleep onset - Total sleep time	- Falls (number of falls and time of occurrence) - Continuous fall risk monitoring

In case of large amount of missing data for a subject within a given period, endpoints might not be derived according to BioSensics procedure and hence the data will be set to missing. Data cleaning and classification will take place prior to database lock.

Additionally, raw data will be made available as sdtm format.

24.1.11 Fall Diary

Assessment of falls during the course the trial will be done using a dedicated MSA fall diary developed by Lundbeck. The diary consists of 12 questions with response options as seen below in Panel 14, with number of falls within the last 24 hours (Q2) being the key outcome for further analysis.

Question 10, 11 and 12 are only to be filled out on a weekly basis and should only occur once a week in the e-diary. However, due to an initial mistake in the set-up, the weekly questions appeared daily and hence several assessments will be available within the same week. In those cases, the Day 7 assessment (related to the Day 1 being the first day an individual fills out the diary within a period) will be the applicable one used for the analysis; meaning that remaining assessments within the same period will be disregarded. The e-diary will be updated and hence this rule will only apply for early patients having multiple entries for the weekly questions within the same week.

Panel 14 Derivation of Fall Diary parameters

Fall Diary question	Specific wording	Response option
Q1	Did you fall in the past 24 hours? (A fall is defined as UNEXPECTANTLY coming to rest on the ground, floor or just a lower level than where you started.)	Yes/No
Q2	How many times did you fall in the past 24 hours?	Number
Q3	What time did you fall?	Time point
Q4	Where were you when you fell?	Indoors / Outdoors
Q5	Was it in a place you know well?	Yes/No
Q6	Did you experience any dizziness, light-headedness, feeling faint or blurred vision before falling?	Yes/No
Q7	Did you experience freezing of gait/movement locking before falling? (Freezing of gait: feeling like your feet were stuck to the ground)	Yes/No
Q8	Did you need somebody's help to get up after you fell?	Yes/No
Q9	Did the fall cause any physical injury?	Yes/No
Q10	During the last week, how many times did you consult a healthcare professional due to a fall? (consider any past falls / whenever the fall happened)	Number
Q11	During the last week, how many times did you visit a hospital due to a fall? (consider any past falls / whenever the fall happened)	Number
Q12	During the last week, how many times did you have an x-ray due to a fall? (consider any past falls / whenever the fall happened)	Number

Number of falls per period

Within each dispense/observation period (BL, V9, V12, V15, and V18) the defined visit windows will be applied to identify valid data entries. Within each period, the total number of falls will be calculated as the sum of the Q2 responses. In addition, an adjusted total number of falls per period will be calculated as the total number of falls divided by the number of days where the Fall Diary was filled out (Q1 NOT missing). The adjusted number of falls per period will be the primary endpoint for further analysis of falls.

24.1.12 Magnetic Resonance Imaging (MRI)

MRI at Screening will be performed for eligibility and, in addition, the presence of MRI abnormalities supporting the diagnosis of MSA (putaminal atrophy, pontine atrophy, cerebellar and middle cerebellar peduncle atrophy, presence of putaminal hyperintense rim, putaminal signal hypointensity and/or hot cross bun sign) will also be recorded.

In addition, MRI scans will be performed for evaluation of biomarkers of disease progression and safety. The scans will be evaluated by a central reader, as pre-specified in the study-specific *Imaging Charter*.

Panel 15 contains an overview for the MRI sequences and derived parameters used for evaluation of disease progression.

Panel 15 Derivation of MRI parameters

MRI sequencing	Description	Regions of interest
Volumetric MRI (vMRI)	Quantification of atrophy measures in brain ROIs	- caudate nucleus - putamen - striatum - pons - brain stem - cerebellum
Diffusion-tensor imaging (DTI)	Quantification of diffusivity measures in brain ROIs	- caudate nucleus - putamen - globus pallidus - pons - cerebellar white matter - middle cerebellar peduncle
Arterial spin label (ASL)	Quantification of cerebral blood flow (CBF) in selected brain regions	- putamen - cerebellum

Additional MRI sequences will be performed for assessment of safety, including 2D T2-weighted, 3D T2 FLAIR, diffusion-weighted imaging and gradient-recalled echo (GRE) sequence. The last will be used to assess the presence of cerebral microhaemorrhages.

The primary analysis for the volumetric parameters will be the percentage-wise change from baseline in each region-of-interest in the actual numbers, whereas numbers normalized by the intercranial volume (head size) will be secondary.

In some instances, an alternative workflow was performed to ensure quality of data. In case where both the original and the re-analyzed value would be present, the re-analyzed value would be the one used for further analyses.

24.2 Assigning Data to Visits

Invalid assessments will be assigned AVISTN = 888. If the date of last dose is missing, assessments will be considered valid. If multiple assessments are taken the same day, only the last assessment will be valid. Invalid assessments will not be considered in descriptive statistics or statistical analyses but will be included in listings of safety variables.

Assessments at ***unscheduled and withdrawal visits*** will be assigned to a target day (AWTARGET) based on days after baseline visit, and to an analysis week (AVISTN = AWTARGET/7). Assessments falling outside a defined visit window will be evaluated and will be deemed invalid (AVISTN = 888) for that specific windowing approach in case no obvious week can be identified.

24.2.1 UMSARS and additional efficacy COAs

For UMSARS, both a narrow and a broad approach will be applied for assigning observations to a visit: 1) observations will be mapped to the nearest official clinical visit in 4-weeks intervals, independent whether UMSARS originally was scheduled for this visit, and 2)

observations will be mapped to the nearest official UMSARS visit in 12-weeks intervals according to protocol.

Panel 16 Visit Windows for UMSARS

Nominal Vis Number (DB-Period)	Nominal Vis Week	Nominal Vis Day	Time Window narrow[1]	Time Window broad[1]
V1 (Screening Visit)	-6	-42	NA	NA
V3 (Baseline Visit)	0	0	-7 to 7	-7 to 7
V5 (WD Visit)	4	28	15 to 42	NA
V7 (WD Visit)	8	56	43 to 69	NA
V9 (planned UMSARS/WD Visit)	12	84	70 to 98	15 to 126
V10 (WD Visit)	16	112	99 to 126	NA
V11 (WD Visit)	20	140	127 to 154	NA
V12 (planned UMSARS/WD Visit)	24	168	155 to 182	127 to 210
V13 (WD Visit)	28	196	183 to 210	NA
V14 (WD Visit)	32	224	211 to 238	NA
V15 (planned UMSARS/WD Visit)	36	252	239 to 266	211 to 294
V16 (WD Visit)	40	280	267 to 294	NA
V17 (WD Visit)	44	308	295 to 322	NA
V18 (planned UMSARS/EoTDBP/WD Visit)	48	336	323 to 350	295 to 378
V19 (EoTDBP/WD Visit)	52	364	351 to 378	NA
V20 (EoTDBP/WD Visit)	56	392	379 to 406	NA
V21 (planned UMSARS/EoTDBP/WD Visit)	60	420	407 to 434	379 to 462
V22 (EoTDBP/WD Visit)	64	448	435 to 462	NA
V23 (EoTDBP/WD Visit)	68	476	463 to 490	NA
V24 (planned UMSARS/EoTDBP Visit)	72	504	491 to 518	463 to 518
Nominal Visit Number (OLE-Period)				
V1E (baseline OLEP Visit)[2]	0E	0	-7 to 7	-7 to 7
V2E (WD Visit)	4E	28	15 to 42	NA
V3E (WD Visit)	8E	56	43 to 69	NA
V4E (planned UMSARS/WD Visit)	12E	84	70 to 98	15 to 126
V5E (WD Visit)	16E	112	99 to 126	NA
V6E (WD Visit)	20E	140	127 to 154	NA
V7E (planned UMSARS/WD Visit)	24E	168	155 to 182	127 to 210
V8E (WD Visit)	28E	196	183 to 210	NA
V9E (WD Visit)	32E	224	211 to 238	NA
V10E (planned UMSARS/WD Visit)	36E	252	239 to 266	211 to 294
V11E (WD Visit)	40E	280	267 to 294	NA
V12E (WD Visit)	44E	308	295 to 322	NA
V13E (planned EoTOLE Visit)	48E	336	323 to 350	295 to 350

All post-baseline visits (except EoT visits) can be converted into a Withdrawal (WD) Visit.
[1] For DBP and OLEP, respectively, the applied narrow window will be continuous (i.e., ±14 days) to avoid invalid assessments (protocol text ±3 days). The broad window is set up as continuous as well to match.
[2] EoTDBP Visit will work as Baseline Visit for the OLEP if done within the acceptable window.

Records to be used in descriptive statistics or statistical analyses will be flagged with ANL01FL=Y and ANL02FL=Y. ANL01FL = Y and ANL02FL=Y will be assigned to all valid assessments (NOMWEEK not equal to 888) unless an assessment at the Withdrawal Visit or an Unscheduled Visit is assigned to the same analysis week as a scheduled visit (having the same NOMWEEK). In this case, ANL01FL = Y will be assigned to one valid visit prioritized in the following order: Scheduled Visit, Unscheduled Visit, and Withdrawal Visit.

CGI-S, PGI-S, and OGI-S will follow the same windowing principles since these were administered at the exact same visits as the UMSARS. The remaining COAs, i.e., SE-ADL, COMPASS Select Change and EQ-5L-5D were only administered at Week 24, 48 and 72 (Visit 12, 18, and 24) post-baseline in the DBP, and hence the broad windowing will only contain these visits using the above intervals, meaning that some observations might be deemed invalid for this mapping. However, they will be mapped into the above narrow windows as well using the continuous windowing approach. The same principles will be applied for the OLEP.

Remission in the CGI-S, PGI-S or OGI-S score (defined as a score of 1 or 2) at each analysis week following a baseline will be included as new parameters (PARAM=*Remission*).

24.2.2 MRI parameters

MRI parameters (volumetric, DTI and ASL) are assessed at the following visits, and hence a broad windowing will only be applied for these visits. A narrow window will also be defined using all per-protocol defined efficacy visits as scheduled in Panel 16 above. Only MRI volumetric will be evaluated in the OLEP.

Panel 17 Visit Windows for MRI

Nominal Vis Number (DB-Period)	Nominal Vis Week	Nominal Vis Day	Time Window narrow[1]	Time Window broad[1]
V3 (Baseline Visit)	0	0	-7 to 7	-7 to 7
V9 (planned MRI Visit)	12	84	70 to 98	15 to 126
V12 (planned MRI Visit)	24	168	155 to 182	127 to 210
V18 (planned MRI Visit)	48	336	323 to 350	295 to 378
V24 (planned UMSARS/EoTDBP Visit)	72	504	491 to 518	463 to 518
Nominal Visit Number (OLE-Period)				
V1E (baseline OLEP Visit)[2]	0E	0	-7 to 7	-7 to 7
V13E (planned EoTOLE Visit)	48E	336	323 to 350	295 to 350

All post-baseline visits (except EoT visits) can be converted into a Withdrawal (WD) Visit.
[1] For DBP and OLEP, respectively, the applied narrow window will be continuous (i.e., ±14 days) to avoid invalid assessments (protocol text ±3 days). The broad window is set up as continuous as well to match.
[2] EoTDBP Visit will work as Baseline Visit for the OLEP if done within the acceptable window.

24.2.3 Blood sampling parameters

For blood sampling for IMP, safety lab (only one performed also at screening), α-synuclein and ADA the following windowing will be applied with the addition of the Visit 6 and the Safety follow-up Visit (SFU).

Panel 18 Visit Windows for Blood Sampling Parameters

Nominal Vis Number (DB-Period)	Nominal Vis Week	Nominal Vis Day	Time Window narrow[1]	Time Window broad[1]
V1 (Screening Visit – planned sampling)	-6	-42	NA	NA
V3 (Baseline Visit – planned sampling)	0	0	-7 to 7	-7 to 7
V5 (planned sampling Visit)	4	28	21 to 35	21 to 35
V6 (planned sampling Visit)	6	42	36 to 49	36 to 49
V7 (planned sampling Visit)	8	56	50 to 69	50 to 69
V9 (planned sampling Visit)	12	84	70 to 98	70 to 126
V10 (WD Visit)	16	112	99 to 126	NA
V11 (WD Visit)	20	140	127 to 154	NA
V12 (planned sampling Visit)	24	168	155 to 182	127 to 210
V13 (WD Visit)	28	196	183 to 210	NA
V14 (WD Visit)	32	224	211 to 238	NA
V15 (planned sampling Visit)	36	252	239 to 266	211 to 294
V16 (WD Visit)	40	280	267 to 294	NA
V17 (WD Visit)	44	308	295 to 322	NA
V18 (planned sampling Visit)	48	336	323 to 350	295 to 378
V19 (EoTDBP/WD Visit)	52	364	351 to 378	NA
V20 (EoTDBP/WD Visit)	56	392	379 to 406	NA
V21 (planned sampling Visit)	60	420	407 to 434	379 to 462
V22 (EoTDBP/WD Visit)	64	448	435 to 462	NA
V23 (EoTDBP/WD Visit)	68	476	463 to 490	NA
V24 (planned sampling EoTDBP/WD Visit)	72	504	491 to 518	463 to 518
V25 (planned sampling SFU Visit)	88	616	609 to 623	595 to 630

Nominal Visit Number (OLE-Period)				
V1E (BL OLEP Visit – planned sampling)[2]	0E	0	-7 to 7	-7 to 7
V2E (WD Visit)	4E	28	15 to 42	NA
V3E (WD Visit)	8E	56	43 to 69	NA
V4E (WD Visit)	12E	84	70 to 98	NA
V5E (WD Visit)	16E	112	99 to 126	NA
V6E (WD Visit)	20E	140	127 to 154	NA
V7E (planned sampling Visit)	24E	168	155 to 182	127 to 210
V8E (WD Visit)	28E	196	183 to 210	NA
V9E (WD Visit)	32E	224	211 to 238	NA
V10E (WD Visit)	36E	252	239 to 266	NA
V11E (WD Visit)	40E	280	267 to 294	NA
V12E (WD Visit)	44E	308	295 to 322	NA
V13E (EoTOLE Visit – planned sampling)	48E	336	323 to 350	295 to 350
SFU-E (planned sampling SFU Visit	64E	448	434 to 462	434 to 462

All post-baseline visits (except EoT visits) can be converted into a Withdrawal (WD) Visit.
[1] For DBP and OLEP, respectively, the applied narrow window will be continuous (i.e., ±14 days) to avoid invalid assessments (protocol text ±3 days). The broad window is set up to allow additional flexibility.
[2] EoTDBP Visit will work as Baseline Visit for the OLEP if done within the acceptable window.

Since CSF sampling for IMP, NfL, t-tau and α-synuclein quantification only is planned for Visit 3 (Baseline), Visit 18 and Visit 72, the above broad windowing will only be applied around these visits. The above narrow windowing will be identical. CSF sampling will not be performed in the OLEP.

Blood sampling for NfL will be assessed at Screening Visit and Baseline Visit Pre-IMP and at Visit 9, 12, 15, 18, 24, 1E, 7E and 13E post-IMP, and hence the above broad windowing will only be applied around these visits. Again, the above narrow windowing will be fully applied in addition.

24.2.4 Vital signs and C-SSRS

Vital signs and C-SSRS assessments will be performed at all DBP and OLEP post-baseline visits except the two Telephone visits (i.e., Visit 4 and Visit 8), and hence only the above narrow windowing will be applied. The C-SSRS will in addition be assessed at the Screening Visit.

24.2.5 Weight

Weight assessments will be performed at the following visits, and hence a broad windowing will only be applied for these visits. A narrow window will also be defined using all per-protocol defined visits as scheduled in Panel 18 above. Weight is not collected in the OLEP.

Panel 19 Visit Windows for Weight

Nominal Vis Number (DB-Period)	Nominal Vis Week	Nominal Vis Day	Time Window narrow[1]	Time Window broad[1]
V1 (Screening Visit – planned eval)	-6	-42	See Panel 16	NA
V3 (Baseline Visit – planned eval)	0	0		-7 to 7
V9 (planned eval Visit)	12	84		50 to 126
V12 (planned eval Visit)	24	168		127 to 210
V15 (planned eval Visit)	36	252		211 to 294
V18 (planned eval Visit)	48	336		295 to 378
V24 (planned eval EoTDBP/WD Visit)	72	504		463 to 518

All post-baseline visits (except EoT visits) can be converted into a Withdrawal (WD) Visit.
[1] For DBP the applied narrow window will be continuous (i.e., ±14 days) to avoid invalid assessments (protocol text ±3 days). The broad window is set up to allow additional flexibility.

24.2.6 ECG

ECG assessments will be performed at the following visits, and hence a broad windowing will only be applied for these visits. A narrow window will also be defined using all per-protocol defined visits as scheduled in Panel 18. ECG is not collected in the OLEP.

Panel 20 Visit Windows for ECG

Nominal Vis Number (DB-Period)	Nominal Vis Week	Nominal Vis Day	Time Window narrow[1]	Time Window broad[1]
V1 (Screening Visit – planned eval)	-6	-42	See Panel 16	NA
V3 (Baseline Visit – planned eval)	0	0		-7 to 7
V6 (planned sampling Visit)	6	42		36 to 49
V12 (planned eval Visit)	24	168		127 to 210
V18 (planned eval Visit)	48	336		295 to 378
V24 (planned eval EoTDBP/WD Visit)	72	504		463 to 518

All post-baseline visits (except EoT visits) can be converted into a Withdrawal (WD) Visit.
[1] For DBP the applied narrow window will be continuous (i.e., ±14 days) to avoid invalid assessments (protocol text ±3 days). The broad window is set up to allow additional flexibility.

24.2.7 Fall Diary

Each Fall Diary period will be defined as the period between the two visits where the diary was supposed to be filled out according to the protocol. Hence, even though this per protocol has been defined as a two-week period for the baseline period and a four-week period for the subsequent periods, the length of each individual period will slightly vary depending on the visit structure for each individual patient. Hence, the following rules will be applied for mapping data into the periods:

Panel 21 Windows for Fall Diary (Periods)

Period (DB-Period)	Start visit	End visit	Planned duration	window around both visits*
Period 0 (Baseline)	Visit 2 (R. visit)	Visit 3 (BL visit)	2 weeks	+/- 3 days
Period 1 (post-IMP)	Visit 7	Visit 9	4 weeks	+/- 3 days
Period 2 (post-IMP)	Visit 11	Visit 12	4 weeks	+/- 3 days
Period 3 (post-IMP)	Visit 14	Visit 15	4 weeks	+/- 3 days
Period 4 (post-IMP)	Visit 17	Visit 18	4 weeks	+/- 3 days

* Fall Diary data available within the acceptable window to be included in the period.

For each period, the data will be mapped into the end visit. Only one windowing approach will be defined around the relevant visits. The Fall Diary data is not collected in the OLEP.

Visit windows for FeetMe and PAMSys devices will be defined on a similar way for consistency.

24.3 Assigning Adverse Events to Analysis Phases

Adverse events will be assigned to an analysis period as follows:

- *Adverse events prior to treatment* – Records not classified as TEAEs will have APHASE= PRETREAT
- *Adverse events in the double-blind period (DBP)* – all TEAEs with date of onset or worsening of intensity/seriousness after first dose of IMP in the DBP and until first dose of IMP in the OLE period (planned for Visit 1E – for patients entering the OLE) or the Safety Follow up visit for the DBP (SFU Visit 25 – for patients NOT entering the OLE) (assigned APHASE = DOUBLE BLIND).
- *Adverse events in the Open-Label Extension period* – TEAEs with date of onset or worsening of intensity/seriousness after first dose of IMP in the OLE period (Visit 1E) and until the final Safety Follow up visit for the OLE (Visit 64E) (assigned APHASE = OLE).

If the start date is missing/incomplete and not eligible for imputation, the TEAE will be assigned to the DOUBLE BLIND phase.

24.4 Handling Missing or Incomplete Dates/Times

24.4.1 IMP Start and Stop Dates

For deriving variables for adverse events and concomitant medication:

- Missing IMP start date will be imputed for enrolled patients by the date of the baseline visit
- Missing IMP stop date will be imputed for enrolled patients by the date of the latest attended visit (scheduled/unscheduled/withdrawal)

For evaluating validity of efficacy assessments:

- Missing IMP stop date will be imputed for enrolled patients by the date of the latest attended visit (scheduled/unscheduled/withdrawal) before the safety follow-up

Exposure will not be calculated for patients with missing IMP start and/or stop dates.

24.4.2 Withdrawal Date

For withdrawn patients with a missing Withdrawal Visit, the date of the last attended visit before safety follow-up will be used in the calculation of time to withdrawal from treatment.

24.4.3 Medication Start and Stop Dates

Concomitant medications with missing start and stop dates will be classified according to the following rulesas determined from the IMP start date. Incomplete dates will be evaluated and compared to IMP start date by imputing the missing information as follows:

- If Day is missing (DD): for start dates, 1 will be used; for end dates, the last day in that respective month, i.e., 28/29/30/31
- If Month is missing (MMM): for start dates: January will be used; for end dates, December will be used
- If Year is missing (YYYY): for start dates: year will be set to the year before IMP start; for end dates, year will be set to the year after last IMP

No duration will be calculated for ongoing medications and for medications with missing/incomplete start date and/or stop date.

24.4.4 Adverse Event Start and Stop Dates

If the start date is missing/incomplete for an adverse event and the stop date is prior to the first dose of IMP, the adverse event will be classified as a pre-treatment adverse event. In all other cases of an adverse event with a missing/incomplete start and/or stop date, the adverse event will be classified as a TEAE. No imputation of start/stop dates will be done, except in the case of adverse events which change in intensity/seriousness. For details on deriving multiple events from change in intensity/seriousness, and corresponding stop- and start dates, see section 24.5.2.

For adverse events ongoing at the end of the study, the date of the last study contact will be used as the stop date for the adverse event in the calculation of duration. For other adverse events with a missing/incomplete start or stop date, the duration will not be calculated.

24.4.5 Diagnosis and Symptom onset Start Dates

Missing start dates for diagnosis and symptom onset will be imputed according to the following rules:

- If Day is missing (DD): The first day of the month will be used, i.e., 01

- If Month is missing (MMM): January will be used, i.e., 01

If both dates are missing hence 01-01 should be used. After imputation, the calculation of both 'time-since-diagnosis' and 'time-since-symptom-onset' should be done in relation to treatment start date (i.e., TRTSDT – DIAGDTC, TRTSDT – SYMPDTC), meaning that if the diagnosis was done within the same year of treatment start, then time-since-diagnosis should be <1.

24.5 Data with Multiple Records

24.5.1 Dose Changes in Medication

Dose changes in medications are recorded on multiple rows in the dataset, with different start and stop dates. When classifying medications into periods (prior to IMP, continued after first dose of IMP, started at or after first dose of IMP), each dose is considered a separate medication, and the same medication can be assigned to several periods for the same patient. Within a period, multiple entries contribute as a single count.

24.5.2 Changes in Intensity or Seriousness of Adverse Events

Changes in adverse event intensity or seriousness are recorded on multiple rows in the dataset. An adverse event that changes in intensity or seriousness will contribute to the count of events as a single event.

In summaries of adverse events presented by intensity, the maximum intensity of the adverse event will be used. The maximum intensity is searched for in events with changes, as well as over repeated events based on the preferred term. For TEAEs and causally related TEAEs, the record(s) with the maximum intensity and maximum related intensity within an analysis phase will be flagged in ADaM data with ASEVMAX=Y and ARSEVMAX=Y, respectively. Adverse events for which information on intensity is missing will be classified as *severe*. Adverse events for which information on seriousness is missing will be classified as *serious*.

During the course of an event, information about all changes in intensity are collected (intensity and start date of intensity change). In ADaM data, changes in intensity are included as additional records (rows) to the originally reported adverse event reflecting the way data are collected. For instance, an adverse event that changes from mild to moderate will have two records, one with intensity mild and one with intensity moderate. Start date for the first intensity will be the start date for the originally reported event. The stop date for the last intensity will be the stop date for the originally reported event, and for the preceding intensities the stop date will be set to the date of reported change in intensity minus 1, or the date of reported change if a change occurring on the same day as the originally reported event, or if there is more than one change on a day.

If an adverse event changes from non-serious to serious, in addition to the originally reported adverse event start date, the start date for the seriousness is reported. However, the event is only reported as serious in the adverse event eCRF. In ADaM data, adverse events that change

from non-serious to serious will be included as two records, one with seriousness non-serious and one with seriousness serious. The start date for the non-serious event will be the start date for the originally reported adverse event, and the stop date will be set to the start date of the seriousness minus 1. The stop date for the serious event will be the stop date for the originally reported adverse event. If an intensity and seriousness is reported on the same date, record will be added reflecting both the change in intensity and seriousness (e.g. for an adverse event originally reported as being mild and non-serious is reported as having changed to severe and serious on the same date, there will be one additional record in data).

Duration (days) will be calculated for each intensity/seriousness based on the intensity/seriousness start-and stop dates. No duration will be calculated for adverse events with incomplete or missing start-or stop date, or for events ongoing at the end of the study.

24.6 Handling Exposure Data

Exposure across the whole study period will be assigned PARAM = 'Study' and exposure within visit intervals will be assigned PARAM = 'V1_V2', PARAM = 'V2_V3', and PARAM = 'V3_V4', etc., for intervals between V1 and V2, V2 and V3, V3 and V4, etc., respectively.

Exposure to dose of Lu AF82422 in the study period is calculated as:
(Date of last dose +28) – (Date of first dose + 1)

Exposure in days will be given in variables EXP1D, EXP2D, EXP3D. Corresponding exposure in years will be given in variables EXP1Y, EXP2Y, EXP3Y derived as exposure in days divided by 365.25.

The average dose in the full study period will be derived.

For the study time-interval the duration of exposure to dose will be categorized into the intervals 1-7 days, 8-14 days, …., etc.

24.7 Handling digital-device data

Data from two digital devices, i.e., FeetMe shoe insoles and BioSensics PAMSys wearable, will be collected throughout the study according to study procedure. Both data sources will have been curated by the vendor prior to integrating into sdtm and hence, relevant parameters have already been derived for the specific periods.

Reference

1 The natural history of multiple system atrophy: a prospective European cohort study, G.K. Wenning et al, Lancet Neurol 2013; 12: 264–74; US ref: Natural history of multiple system atrophy in the USA: a prospective cohort study, P.A. Law et al, Lancet Neurol 2015; 14: 710–19

2 The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model, R. J. Bateman et al., Alzheimer's & Dementia 13 (2017) 8-19.

3 A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease, G. Wang et al., Statistics in Medicine. 2018;1–9.

4 Developing a Natural History Progression Model for Duchenne Muscular Dystrophy Using the Six-Minute Walk Test, L. Hamuro et al., CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 596–603.

5 Bayesian model of disease progression in GNE myopathy, M. Quintana et al., Statistics in Medicine. 2019; 38:1459–1474.

6 Natural cubic splines for the analysis of Alzheimer's clinical trials, M. Donohue et al, Pharmaceutical Statistics. 2023;1‑12.

Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Trial title:	Interventional, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study to assess the efficacy, safety and tolerability of Lu AF82422 in patients with Multiple System Atrophy
Trial No.:	18331A
SAP date:	20 December 2023

This document has been signed electronically. The signatories are listed below.

Authentication

Biostatistician: PPD

Clinical research: PPD

Authorization

Head of Biostatistics: PPD

Appendix II

SAS® Code

SAS® Code

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Appendix III
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Appendix IV
Study Flow Chart

Study Flow Chart

Table 1 Study Procedures and Assessments - Double-blind Treatment Period

Visit Name	Screening	Randomization	Baseline + IMP	Telephone Visit	IMP	Site Visit	IMP	Telephone Visit	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	EoT/Withdrawal[b]	SFU[c]
Visit Number	**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**
Week[d]	**6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**88**
Visit Window[e] (days relative to nominal visit)		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**
Screening/Randomization Procedures and Assessments																									
Signed informed consent	√																								
Demographics (age, sex, race)	√																								
MSA diagnostic criteria: Possible or probable, MSA-P or MSA-C	√																								
MSA History	√																								
MoCA	√																								
Relevant medical history (e.g., psychiatric, neurological)	√																								
Recent and on-going medication	√																								
Height	√																								
Blood sampling for pregnancy test	√																								
MRI scan for eligibility[f]	√																								
Inclusion/exclusion criteria	√	√																							
Signs and symptoms present at SCR, Randomization and/or BL (before IMP administration; recorded on an *Adverse Event Form*)	√	√	√																						
Randomization		√																							
Efficacy Assessments																									
UMSARS	√		√						√			√			√			√			√			√	
SE-ADL			√									√						√						√	
COMPASS Select			√																						
COMPASS Select Change												√						√						√	
CGI-S			√						√			√			√			√			√			√	
PGI-S			√						√			√			√			√			√			√	
OGI-S			√						√			√			√			√			√			√	

Visit Name	Screening	Randomization	Baseline + IMP	Telephone Visit	IMP	Site Visit	IMP	Telephone Visit	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	EoT/Withdrawal[b]	SFU[c]
Visit Number	**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**
Week[d]	**6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**88**
Visit Window[e] (days relative to nominal visit)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**
Fall diary, daily recording		√[g]	√[h]				√[g]		√[h]		√[g]	√[h]		√[g]	√[h]		√[g]	√[h]							
FeetMe® (subset) optional[x]		√[i]	√[j]				√[i]		√[j]		√[i]	√[j]		√[i]	√[j]		√[i]	√[j]							
PAMSys (subset) optional[x]		√[i]	√[j]				√[i]		√[j]		√[i]	√[j]		√[i]	√[j]		√[i]	√[j]							
MRI scan: vMRI, DTI and ASL measures[v,w]			√						√			√						√						√[t]	
CSF sampling[k] for NfL and t-tau			√															√						√[u]	
Blood sampling for NfL	√		√						√			√			√			√						√	
Quality of Life Assessments																									
EQ-5D-5L			√									√						√						√	
Pharmacokinetic Assessments																									
Blood sampling for IMP quantification[l]			√[l]		√	√	√		√[l]			√			√[l]			√			√			√	√
CSF sampling[k] for IMP quantification			√															√						√[u]	
Target Engagement Assessments																									
CSF sampling[k] for α-synuclein and pathological species of α-synuclein			√															√						√[u]	
Blood sampling for α-synuclein[l]			√[l]		√	√	√		√[l]			√			√[l]			√			√			√	√
Safety Assessments																									
Adverse events			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Follow-up of adverse events on-going at EoT or withdrawal, and new AEs and SAEs																									√
Blood and urine sampling for clinical safety laboratory tests	√		√		√	√	√		√			√			√			√			√			√	√
Blood sampling for ADAs			√		√	√	√		√			√			√			√			√			√	√
Vital signs[m]			√		√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Weight	√		√						√			√			√			√						√	
Examinations (physical, neurological)[n]	√		√		√	√			√			√			√			√						√	
ECG	√		√			√						√						√						√	
MRI scan for safety[w]			√						√			√						√						√[t]	
C-SSRS[o]	√		√		√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Visit Name	Screening	Randomization	Baseline + IMP	Telephone Visit	IMP	Site Visit	IMP	Telephone Visit	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	IMP/EoT[a]	EoT/Withdrawal[b]	SFU[c]
Visit Number	**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**
Week[d]	**6**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**	**64**	**68**	**72**	**88**
Visit Window[e] (days relative to nominal visit)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**
Biobanking																									
Blood sampling for gene expression profiling (RNA)[p]			√									√						√							
Blood sampling for metabolomics/proteomics (plasma)[p]			√									√						√							
Blood sampling for pharmacogenetics (DNA) (optional)[q]			√																						
Blood sampling for ADA			√		√	√	√		√			√			√			√			√			√	√
CSF sampling[k]			√															√						√[u]	
Other Study Procedures and Assessments																									
IMP administration[m]			√		√		√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Concomitant medication (prescription and non-prescription)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test, urine dipstick[r]		√	√		√		√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Exit interview (subset)[s]																								√	

ADA = Anti-Drug Antibody; AE = adverse event; ASL = arterial spin label; BL = baseline; CGI-S = Clinical Global Impression – Severity of Illness; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; COMPASS = Composite Autonomic System Score; DNA = deoxyribonucleic acid; DTI = diffusion-tensor imaging; ECG = electrocardiogram; EoT = End-of-Treatment; EQ-5D-5L = Euroqol 5 Dimensions-5 Levels; IMP = investigational medicinal product; IRT = Interactive Response Technology; MoCA = Montreal Cognitive Assessment; MSA-C = Multiple System Atrophy with predominant cerebellar features; MSA-P = Multiple System Atrophy with predominant parkinsonism; MRI = magnetic resonance imaging; NfL = Neurofilament Light chain; OGI-S = Observer-rated Global Impression-Severity of Illness; PGI-S = Patient Global Impression-Severity of Illness; SAE = serious adverse event; SE-ADL = Schwab & England Activities of Daily Living; SFU = Safety Follow-up of DBP; SCR = screening; T-tau = total tau; UMSARS = Unified Multiple System Atrophy Rating Scale; vMRI = volumetric magnetic resonance imaging

a. When the last patient randomized reaches Visit 18/Week 48, the remaining patients in the double-blind treatment period will have their next scheduled visit converted to an EoT Visit (assessments as listed for Visit 24, no IMP administration).

b. Patients who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible.

c. The Safety Follow-up Visit will take place 20 weeks after last IMP administration. This will apply only to patients who do not enter the OLE or if timing of the safety FU will be before their first visit in the OLE.

d. All assessments may be completed over a maximum of 2 consecutive days (except for MRI, see footnote w); if so, the first day is considered the "visit" day according to the schedule and at IMP Visits, IMP must be registered in IRT and administered on the second day. The Screening Visit can be performed over 2 days during the first week of the Screening Period.

e. If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to screening for Visit 2 and Visit 3 and relative to baseline for visits after baseline.

f. MRI scan for eligibility can be performed between Visit 1 and Visit 2. The MRI scan should be uploaded for central reading no later than ten calendar days before the Randomization Visit.

g. Dispense fall diary. This does not apply to a patient who scores 4 on UMSARS Part I item 7 (walking) or if the patient is wheelchair bound for unrelated disorders. This needs to be evaluated at each visit, where the fall diary is dispensed.

h. Return of the fall diary. Patients who withdraw during a period with fall diary entries must return the diary at the Withdrawal Visit.

i. Sensor subset: at the US sites, the patients can participate in an optional objective sensor-based assessments subset. The patients undergoing the additional objective sensor-based assessments must provide specific consent as part of the main *Informed Consent Form*. The patient does not have to consent to both objective sensor-based assessments to participate. The sensor(s) will be applied during the clinic visit. The use of the sensors does not apply to a patient who scores 4 on UMSARS Part I item 7 (walking) or if the patient is wheelchair bound for unrelated disorders. This needs to be evaluated at each visit, where the sensors are dispensed.

j. Return of the sensor(s). Patients who withdraw during a period with objective sensor-based assessments must return the sensor(s) at the Withdrawal Visit.

k. CSF sampling not applicable for patients with contraindications of lumbar puncture, history of severe post-lumbar puncture headache, on-going skin infection at the lumbar puncture injection site or documented history of vertebral deformities, major lumbar back surgery, clinically significant back pain, clinically significant abnormal x-ray, and/or injury that, in the opinion of the investigator, would preclude CSF collection. CSF sampling, when performed at baseline, should be completed prior to IMP administration.

l. Multiple samples to be taken relative to IMP infusion: before infusion (at the same time as sampling for clinical safety laboratory tests), immediately after the end of infusion (EOI), 1 and 2 hours after EOI at baseline, Week 12 and Week 36. At all other visits with blood PK and α-synuclein sampling, samples will be taken before infusion.

m. Blood pressure and pulse will be measured immediately prior to IMP administration and patients will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes (±5 minutes) or until stable, whichever is later.

n. Including recording of use of feeding tube and/or wheelchair.

o. Different versions will be used: 'Baseline/Screening' version at Visit 1 and at Visit 3 and 'Since last visit' version at subsequent visits.

p. Exploratory gene expression profiling (RNA) and metabolomics/proteomics are an integrated part of the study and are covered by the main *Informed Consent Form.*

q. Sampling for pharmacogenetics is optional and a separate signed *Informed Consent Form* must be in place to cover this analysis.

r. If positive, confirm with serum pregnancy test.

s. Exit Interview subset: at the US sites, the patients and caregivers will undergo the Exit interviews via telephone or web conferencing platform (e.g., Microsoft Teams). The Exit interview will be conducted within 3 weeks after the EoT Visit or within 3 weeks after the Withdrawal Visit for patients who reach a 48-week treatment period but withdraw prior to the EoT Visit. Study Experience Interview subset: at US sites, a subset of patients and caregivers may be contacted to participate in a Study Experience interview by telephone or web conferencing platform (e.g., Microsoft Teams). The Study Experience interview will be conducted within 6 weeks after the completed Exit interview for patients who consent.

t. MRI scanning only to be performed as EoT/withdrawal procedure if not performed within the last 8 weeks.

u. CSF sampling only to be performed as withdrawal procedure in case of withdrawal prior to Visit 18/Week 48 and for patients with EoT at Visit 18/Week 48. Patients with EoT after Visit 18/Week 48 will not undergo CSF sampling as part of the EoT procedures.

v. DTI and ASL measures where available. If Visit 3 MRI scanning is performed without DTI and/or ASL sequences and these sequences are implemented in the scanner at a later stage, DTI and ASL should not be performed at subsequent visits with MRI measurements.

w. MRI scan can be performed any day within the Visit Window, except for Visit 3 where it must be performed before IMP administration. Date of MRI scan will not define Day 1 or Day 2 of a visit and will not be regarded as a separate visit.

x. Participation in FeetMe® and PAMSys subsets are optional, but informed consent for these are part of the main informed consent. The use of the sensors does not apply to a patient who scores 4 on UMSARS Part I item 7 (walking) or if the patient is wheelchair bound for unrelated disorders. This needs to be evaluated at each visit, where the sensors are to be dispensed.

Table 2 Optional Open-label Long-term Extension Treatment Period

Visit Name	Baseline - IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	End of Open-Label Treatment	Withdrawal[a]	Safety Follow-up[b]
Visit Number	1E	2E	3E	4E	5E	6E	7E	8E	9E	10E	11E	12E	13E	WD	SFU-E
Week[c]	0E	4E	8E	12E	16E	20E	24E	28E	32E	36E	40E	44E	48E		64E
Visit Window[d] (days relative to nominal visit)		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±7
Signed informed consent	√														
Efficacy Assessments															
UMSARS	√[e]			√			√			√			√	√	
CGI-S	√[e]			√			√			√			√	√	
PGI-S	√[e]			√			√			√			√	√	
SE-ADL	√[e]						√						√	√	
EQ-5D-5L	√[e]						√						√	√	
MRI scans: vMRI[f]	√[e,g]												√	√	
Blood sampling for NfL	√						√						√	√	
Pharmacokinetic Assessments															
Blood sampling for IMP quantification	√[e]						√						√	√	√
Pharmacodynamic Assessments															
Blood sampling for α-synuclein	√[e]						√						√	√	√
Safety Assessments															
Adverse events	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Blood and urine sampling for clinical safety laboratory tests	√[e]						√						√	√		
Vital signs[h]	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Examinations[i] (physical, neurological)	√[e]						√						√	√		
C-SSRS since last visit	√[e]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Biobanking																
Blood sampling for ADA	√[e]						√						√	√	√	
Other Study Procedures and Assessments																
IMP administration[h]	√	√	√	√	√	√	√	√	√	√	√	√				
Concomitant medication	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Urine pregnancy test[j]	√[e]	√	√	√	√	√	√	√	√	√	√	√	√	√	-	

ADA = Anti-Drug Antibody; CGI-S = Clinical Global Impression – Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = Euroqol 5 Dimensions-5 Levels; IMP = investigational medicinal product; PGI-S = Patient Global Impression-Severity of Illness; SE-ADL: Schwab & England Activities of Daily Living; SFU-E = Safety Follow-up OLE; UMSARS = Unified Multiple System Atrophy Rating Scale; vMRI = volumetric magnetic resonance imaging; WD = withdrawal

a Participants who withdraw, except for those who withdraw their consent, will be asked to attend a Withdrawal Visit as soon as possible.

b The Safety Follow-up Visit will take place 16 weeks after Visit 13E / 20 weeks after last IMP administration in case of withdrawal (follow-up of adverse events on-going at EoT or withdrawal, and new AEs and SAEs).

b All assessments may be completed over a maximum of 2 days (except for MRI, see footnote e); if so, the first day is considered the "visit" day according to the schedule and at IMP visits, IMP must be registered in IRT and administered on the second day.

d If the date of a visit does not conform to the schedule, subsequent visits should be planned to maintain the visit schedule relative to Visit 1E. o

e Only applicable for patients who enter the OLE more than 1 week later as the EoT Visit in the double-blind treatment period.

f MRI scan can be performed any day within the Visit Window. Date of MRI scan will not define Day 1 or Day 2 of a visit and will not be regarded as a separate visit.

g MRI scanning only to be performed as Visit 1E if not performed within the last 8 weeks.

h Blood pressure and pulse will be measured immediately prior to IMP administration and patients will be monitored after IMP administration for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes (±5 minutes) or until stable, whichever is later.

i Including recording of use of feeding tube and/or wheelchair.

j Only for women of childbearing potential. If positive, confirm with serum pregnancy test.

Appendix V
PCS Criteria

PCS Criteria

Table 3 PCS Criteria for Clinical Safety Laboratory Tests

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
Haematology / Coagulation				
B-haemoglobin	HGB	g/L	≤ 95 (women) ≤ 115 (men)	≥ 165 (women) ≥ 185 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women) ≤ 3.8 (men)	≥ 6.0 (women) ≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women) ≤ 0.37 (men)	≥ 0.50 (women) ≥ 0.55 (men)
B-MCV (mean cell volume)	MCV	fL	≤ 0.8 x LLN	≥ 1.2 x ULN
B-total leucocyte (white cell count)	WBC	x 10E9/L	≤ 2.8	≥ 16
B-neutrophils/leucocytes	NEUTLE	%	≤ 20	≥ 85
B-eosinophils/leucocytes	EOSLE	%		≥ 10
B-basophils/leucocytes	BASOLE	%		≥ 10
B-lymphocytes/leucocytes	LYMLE	%	≤ 10	≥ 75
B-monocytes/leucocytes	MONOLE	%		≥ 15
B-thrombocytes (platelet count)	PLAT	x 10E9/L	≤ 75	≥ 600
P-INR (prothrombin ratio)	INR	Ratio		≥ 2.0
B-prothrombin time	PT	Sec		≥ 18
Liver				
S-aspartate aminotransferase	AST	U/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	U/L		≥ 3 × ULN
S-bilirubin	BILI	µmol/L		≥ 34
S-bilirubin, direct	BILDIR	µmol/L		≥ 12
S-bilirubin, indirect	BILIND	µmol/L		≥ 22
S-alkaline phosphatase	ALP	U/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	U/L		≥ 200
S-alpha-glutathione S-transferase (alpha-GST)	GSTAL	µg/L		≥ 20
Kidney				
S-creatinine	CREAT	µmol/L		≥ 1.5 x ULN
B-urea nitrogen (BUN)	BUN	mmol/L		≥ 11
S-uric acid (urate)	URATE	µmol/L		≥ 510 (women) ≥ 630 (men)
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
S-calcium	CA	mmol/L	≤ 1.8	≥ 3.0
S-chloride	CL	mmol/L	≤ 90	≥ 117
S-magnesium	MG	mmol/L	≤ 0.6	≥ 1.3
S-phosphate (phosphorus, (inorganic)	PHOS	mmol/L	≤ 0.65	≥ 1.95
S-bicarbonate	BICARB	mmol/L	≤ 12	≥ 38
Endocrine / Metabolic				
B-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.4	≥ 9.4
B-glucose, fasting	GLUC	mmol/L	≤ 3.0	≥ 6.0
S-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.9	≥ 11.1
S-glucose, fasting	GLUC	mmol/L	≤ 3.5	≥ 7.0
B-glycosylated haemoglobin, fasting	HBA1C	Hb fract.		≥ 0.065
S-prolactin	PROLCTN	mIU/L		≥ 1350
S-thyrotropin/TSH	TSH	mIU/L	≤ 0.3	≥ 5.5
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L		≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L		≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L		≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L		≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L		≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L		≥ 4.9
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	
S-HDL cholesterol, fasting	HDL	mmol/L	≤ 0.9	
Cardiac/Skeletal/Muscle				
S-creatine kinase (total)	CK	U/L		≥ 400 (women) ≥ 750 (men)
S-creatine kinase MB isoenzyme	CKMB	µg/L		≥ 8.5 or
	CKMBCK	%		≥ 3.5% of total CK
S-lactate dehydrogenase (total)	LDH	IU/L		≥ 750
S-troponin I	TROPONI	µg/L		≥ 1.5
S-troponin T	TROPONT	µg/L		≥ 0.4
Infection				
S-C-reactive protein	CRP	mg/L		≥ 25
S-globulin (total)	GLOBUL	g/L	≤ 15	≥ 55
Urine				

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
Urinary pH	PH		≤ 4	≥ 9

S=serum; B=whole blood; U=urine

Table 4 PCS Criteria for Vital Signs, Weight/BMI, and Waist Circumference

Variable	CDISC Term	Unit	PCS Low	PCS High
Waist circumference	WSTCIR	Cm	decrease ≥ 7%	increase ≥ 7%
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure	OBP	mmHg	≤ -30	
Orthostatic pulse rate	OPR	beats/min		≥ 20
Temperature	TEMP	ºC	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value.

Table 5 PCS Criteria for ECG Parameters

ECG Parameter	CDISC Term	Unit	PCS Low	PCS High
Absolute Time Interval				
PR interval	PRAG	Msec		≥ 260
QRS interval	QRSAG	Msec		≥ 150
QT interval	QTAG	Msec		≥ 500
Derived Time Interval				
Heart rate	EGHRMN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCBAG	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCFAG	Msec	< 300	> 500 or increase > 60

Increase/decrease is relative to the baseline value.

Appendix VI

Definition of Hypersensitivity related reactions

Definition of Hypersensitivity related reactions

Type I hypersensitivity reaction: Anaphylaxis

SEARCH: TEAEs with a PT within the SMQ of Hypersensitivity (narrow scope)

Hypersensitivity (SMQ):	
Acquired C1 inhibitor deficiency	10081035
Acute generalised exanthematous pustulosis	10048799
Administration related reaction	10069773
Administration site dermatitis	10075096
Administration site eczema	10075099
Administration site hypersensitivity	10075102
Administration site rash	10071156
Administration site recall reaction	10075964
Administration site urticaria	10075109
Administration site vasculitis	10075969
AGEP-DRESS overlap	10089003
Allergic bronchitis	10052613
Allergic colitis	10059447
Allergic cough	10053779
Allergic cystitis	10051394
Allergic eosinophilia	10075185
Allergic gastroenteritis	10075308
Allergic hepatitis	10071198
Allergic keratitis	10057380
Allergic lymphangitis	10086007
Allergic oedema	10060934
Allergic otitis externa	10075072
Allergic otitis media	10061557
Allergic pharyngitis	10050639
Allergic reaction to excipient	10078853
Allergic respiratory disease	10063532
Allergic respiratory symptom	10063527
Allergic sinusitis	10049153
Allergic stomatitis	10079554
Allergic transfusion reaction	10066173
Allergy alert test positive	10075479
Allergy test positive	10056352
Allergy to immunoglobulin therapy	10074079
Allergy to surgical sutures	10077279
Allergy to vaccine	10055048

Anal eczema	10078682
Anaphylactic reaction	10002198
Anaphylactic shock	10002199
Anaphylactic transfusion reaction	10067113
Anaphylactoid reaction	10002216
Anaphylactoid shock	10063119
Anaphylaxis treatment	10002222
Angioedema	10002424
Antiallergic therapy	10064059
Antiendomysial antibody positive	10065514
Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
Application site dermatitis	10003036
Application site eczema	10050099
Application site hypersensitivity	10063683
Application site rash	10003054
Application site recall reaction	10076024
Application site urticaria	10050104
Application site vasculitis	10076027
Arthritis allergic	10061430
Atopic cough	10081492
Atopy	10003645
Blepharitis allergic	10005149
Blood immunoglobulin E abnormal	10005589
Blood immunoglobulin E increased	10005591
Bone cement allergy	10087325
Bromoderma	10006404
Bronchospasm	10006482
Bullous haemorrhagic dermatosis	10083809
Catheter site dermatitis	10073992
Catheter site eczema	10073995
Catheter site hypersensitivity	10073998
Catheter site rash	10052271
Catheter site urticaria	10052272
Catheter site vasculitis	10074014
Chronic eosinophilic rhinosinusitis	10071399
Chronic hyperplastic eosinophilic sinusitis	10071380
Circulatory collapse	10009192
Circumoral oedema	10052250
Circumoral swelling	10081703
Conjunctival oedema	10010726
Conjunctivitis allergic	10010744
Contact stomatitis	10067510
Contrast media allergy	10066973
Contrast media reaction	10010836

Corneal oedema	10011033
Cross sensitivity reaction	10011411
Cutaneous vasculitis	10011686
Dennie-Morgan fold	10062918
Dermal filler reaction	10086476
Dermatitis	10012431
Dermatitis acneiform	10012432
Dermatitis allergic	10012434
Dermatitis atopic	10012438
Dermatitis bullous	10012441
Dermatitis contact	10012442
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalised	10012456
Dermatitis herpetiformis	10012468
Dermatitis infected	10012470
Dermatitis psoriasiform	10058675
Device allergy	10072867
Dialysis membrane reaction	10076665
Distributive shock	10070559
Documented hypersensitivity to administered product	10076470
Drug eruption	10013687
Drug hypersensitivity	10013700
Drug provocation test	10074350
Drug reaction with eosinophilia and systemic symptoms	10073508
Eczema	10014184
Eczema infantile	10014198
Eczema nummular	10014201
Eczema vaccinatum	10066042
Eczema vesicular	10058681
Eczema weeping	10055182
Encephalitis allergic	10056387
Encephalopathy allergic	10014627
Eosinophilic granulomatosis with polyangiitis	10078117
Epidermal necrosis	10059284
Epidermolysis	10053177
Epidermolysis bullosa	10014989
Epiglottic oedema	10015029
Erythema multiforme	10015218
Erythema nodosum	10015226
Exfoliative rash	10064579
Eye allergy	10015907
Eye oedema	10052139
Eye swelling	10015967
Eyelid oedema	10015993

Face oedema	10016029
Fixed eruption	10016741
Generalised bullous fixed drug eruption	10084905
Giant papillary conjunctivitis	10018258
Gingival oedema	10049305
Gingival swelling	10018291
Gleich's syndrome	10066837
Haemorrhagic urticaria	10059499
Hand dermatitis	10058898
Henoch-Schonlein purpura	10019617
Henoch-Schonlein purpura nephritis	10069440
Heparin-induced thrombocytopenia	10062506
Hypersensitivity	10020751
Hypersensitivity myocarditis	10081004
Hypersensitivity pneumonitis	10081988
Hypersensitivity vasculitis	10020764
Idiopathic urticaria	10021247
Immediate post-injection reaction	10067142
Immune thrombocytopenia	10083842
Immune tolerance induction	10070581
Implant site dermatitis	10063855
Implant site hypersensitivity	10063858
Implant site rash	10063786
Implant site urticaria	10063787
Incision site dermatitis	10073168
Incision site rash	10073411
Infusion related hypersensitivity reaction	10082742
Infusion related reaction	10051792
Infusion site dermatitis	10065458
Infusion site eczema	10074850
Infusion site hypersensitivity	10065471
Infusion site rash	10059830
Infusion site recall reaction	10076085
Infusion site urticaria	10065490
Infusion site vasculitis	10074851
Injection related reaction	10071152
Injection site dermatitis	10022056
Injection site eczema	10066221
Injection site hypersensitivity	10022071
Injection site rash	10022094
Injection site recall reaction	10066797
Injection site urticaria	10022107
Injection site vasculitis	10067995
Instillation site hypersensitivity	10073612

Instillation site rash	10073622
Instillation site urticaria	10073627
Interstitial granulomatous dermatitis	10067972
Intestinal angioedema	10076229
Iodine allergy	10052098
Kounis syndrome	10069167
Laryngeal oedema	10023845
Laryngitis allergic	10064866
Laryngospasm	10023891
Laryngotracheal oedema	10023893
Limbal swelling	10070492
Lip oedema	10024558
Lip swelling	10024570
Mast cell activation syndrome	10075217
Mast cell degranulation present	10076606
Medical device site dermatitis	10075572
Medical device site eczema	10075575
Medical device site hypersensitivity	10075579
Medical device site rash	10075585
Medical device site recall reaction	10076140
Medical device site urticaria	10075588
Mouth swelling	10075203
Mucocutaneous rash	10056671
Multiple allergies	10028164
Nephritis allergic	10029120
Nikolsky's sign	10029415
Nodular rash	10075807
NSAID exacerbated respiratory disease	10087423
Nutritional supplement allergy	10084049
Oculomucocutaneous syndrome	10030081
Oculorespiratory syndrome	10067317
Oedema mouth	10030110
Oral allergy syndrome	10068355
Oropharyngeal blistering	10067950
Oropharyngeal oedema	10078783
Oropharyngeal spasm	10031111
Oropharyngeal swelling	10031118
Palatal oedema	10056998
Palatal swelling	10074403
Palisaded neutrophilic granulomatous dermatitis	10068809
Palpable purpura	10056872
Pathergy reaction	10074332
Penile dermatitis	10087419
Perioral dermatitis	10034541

Periorbital dermatitis	10087203
Periorbital oedema	10034545
Periorbital swelling	10056647
Pharyngeal oedema	10034829
Pharyngeal swelling	10082270
Polymers allergy	10086347
Procedural shock	10080894
Pruritus allergic	10063438
Puncture site rash	10087940
Radioallergosorbent test positive	10037789
Rash	10037844
Rash erythematous	10037855
Rash follicular	10037857
Rash macular	10037867
Rash maculo-papular	10037868
Rash maculovesicular	10050004
Rash morbilliform	10037870
Rash neonatal	10037871
Rash papulosquamous	10037879
Rash pruritic	10037884
Rash pustular	10037888
Rash rubelliform	10057984
Rash scarlatiniform	10037890
Rash vesicular	10037898
Reaction to azo-dyes	10037973
Reaction to colouring	10037974
Reaction to excipient	10079925
Reaction to flavouring	10082681
Reaction to food additive	10037977
Reaction to preservatives	10064788
Reaction to sweetener	10086454
Rhinitis allergic	10039085
Scleral oedema	10057431
Scleritis allergic	10051126
Scrotal dermatitis	10083260
Scrotal oedema	10039755
Serum sickness	10040400
Serum sickness-like reaction	10040402
Shock	10040560
Shock symptom	10040581
SJS-TEN overlap	10083164
Skin necrosis	10040893
Skin reaction	10040914
Skin test positive	10040934

Solar urticaria	10041307
Solvent sensitivity	10041316
Stevens-Johnson syndrome	10042033
Stoma site hypersensitivity	10074509
Stoma site rash	10059071
Swelling face	10042682
Swelling of eyelid	10042690
Swollen tongue	10042727
Symmetrical drug-related intertriginous and flexural exanthema	10078325
Systemic contact dermatitis	10087943
Tattoo associated skin reaction	10087549
Tongue oedema	10043967
Toxic epidermal necrolysis	10044223
Toxic skin eruption	10057970
Tracheal oedema	10044296
Type I hypersensitivity	10045240
Type II hypersensitivity	10054000
Type III immune complex mediated reaction	10053614
Type IV hypersensitivity reaction	10053613
Urticaria	10046735
Urticaria cholinergic	10046740
Urticaria chronic	10052568
Urticaria contact	10046742
Urticaria papular	10046750
Urticaria physical	10046751
Urticaria pigmentosa	10046752
Urticaria vesiculosa	10046755
Urticarial dermatitis	10082290
Urticarial vasculitis	10048820
Vaccination site dermatitis	10069477
Vaccination site eczema	10076161
Vaccination site exfoliation	10069489
Vaccination site hypersensitivity	10068880
Vaccination site rash	10069482
Vaccination site recall reaction	10076188
Vaccination site urticaria	10069622
Vaccination site vasculitis	10076191
Vaccination site vesicles	10069623
Vaginal ulceration	10046943
Vancomycin infusion reaction	10086737
Vascular access site dermatitis	10085938
Vascular access site eczema	10085939
Vasculitic rash	10047111
Vernal keratoconjunctivitis	10081000

Vessel puncture site rash	10077117
Vessel puncture site vesicles	10077813
Vulval eczema	10066273
Vulval ulceration	10047768
Vulvovaginal rash	10071588
Vulvovaginal ulceration	10050181
Vulvovaginitis allergic	10080783

Type II hypersensitivity reaction: Cytokine Release Syndrome (CRS)

SEARCH: TEAEs with the PT 'Cytokine release syndrome'

Type III hypersensitivity reaction: Immune-complex related reactions

SEARCH: TEAEs with a PT within the SMQ Vasculitis (narrow scope), or with the 15 defined PTs

Vasculitis (SMQ):	
Acute haemorrhagic oedema of infancy	10070599
Administration site vasculitis	10075969
Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
Aortitis	10002921
Application site vasculitis	10076027
Arteritis	10003230
Arteritis coronary	10003232
Behcet's syndrome	10004213
Capillaritis	10068406
Central nervous system vasculitis	10081778
Cerebral arteritis	10008087
Chronic pigmented purpura	10072726
Cogan's syndrome	10056667
Cutaneous vasculitis	10011686
Diabetic arteritis	10077357
Diffuse vasculitis	10012978
Eosinophilic granulomatosis with polyangiitis	10078117
Erythema induratum	10015213
Giant cell arteritis	10018250
Granulomatosis with polyangiitis	10072579
Haemorrhagic occlusive retinal vasculitis	10085070
Haemorrhagic vasculitis	10071252
Henoch-Schonlein purpura	10019617
Henoch-Schonlein purpura nephritis	10069440
Hypersensitivity vasculitis	10020764

Infusion site vasculitis	10074851
Injection site vasculitis	10067995
Kawasaki's disease	10023320
Langerhans' cell histiocytosis	10069698
Lupus vasculitis	10058143
MAGIC syndrome	10078132
Medical device site vasculitis	10076146
Microscopic polyangiitis	10063344
Nodular vasculitis	10029491
Ocular vasculitis	10066926
Polyarteritis nodosa	10036024
Polymyalgia rheumatica	10036099
Pseudovasculitis	10065255
Pulmonary vasculitis	10037457
Radiation vasculitis	10074671
Renal arteritis	10038373
Renal vasculitis	10038546
Retinal occlusive vasculitis	10085059
Retinal vasculitis	10038905
Rheumatoid vasculitis	10048628
Segmented hyalinising vasculitis	10067527
Takayasu's arteritis	10043097
Thromboangiitis obliterans	10043540
Type 2 lepra reaction	10070517
Urticarial vasculitis	10048820
Vaccination site vasculitis	10076191
Vascular purpura	10047097
Vasculitic rash	10047111
Vasculitis	10047115
Vasculitis gastrointestinal	10048319
Vasculitis necrotising	10047124
Viral vasculitis	10056281

Single items PTs:
Glomerulonephritis
Glomerulonephritis acute
Glomerulonephritis chronic
Glomerulonephritis membranoproliferative
Glomerulonephritis membranous
Glomerulonephritis proliferative
Glomerulonephritis rapidly progressive
Mesangioproliferative glomerulonephritis
Immunotactoid glomerulonephritis
Fibrillary glomerulonephritis
Membranous-like glomerulopathy with masked IgG-kappa deposits
Immune-mediated nephritis
Serum sickness
Immune complex level increased
Type III immune complex mediated reaction

Appendix VII

Definition of Concomitant Medication Category

Definition of Concomitant Medication Category

Name	ATC code	Category
etanautine	N04AB01	anti-parkinson medication
orphenadrine (chloride)	N04AB02	anti-parkinson medication
trihexyphenidyl	N04AA01	anti-parkinson medication
biperiden	N04AA02	anti-parkinson medication
biperiden	N04AA02	anti-parkinson medication
metixene	N04AA03	anti-parkinson medication
procyclidine	N04AA04	anti-parkinson medication
procyclidine	N04AA04	anti-parkinson medication
profenamine	N04AA05	anti-parkinson medication
dexetimide	N04AA08	anti-parkinson medication
dexetimide	N04AA08	anti-parkinson medication
phenglutarimide	N04AA09	anti-parkinson medication
mazaticol	N04AA10	anti-parkinson medication
bornaprine	N04AA11	anti-parkinson medication
tropatepine	N04AA12	anti-parkinson medication
benzatropine	N04AC01	anti-parkinson medication
etybenzatropine	N04AC02	anti-parkinson medication
neostigmine	N07AA01	Autonomic dysfunction medication
neostigmine	N07AA01	Autonomic dysfunction medication
pyridostigmine	N07AA02	Autonomic dysfunction medication
pyridostigmine	N07AA02	Autonomic dysfunction medication
distigmine	N07AA03	Autonomic dysfunction medication
distigmine	N07AA03	Autonomic dysfunction medication
ambenonium	N07AA30	Autonomic dysfunction medication
neostigmine, combinations	N07AA51	Autonomic dysfunction medication
tolcapone	N04BX01	anti-parkinson medication
entacapone	N04BX02	anti-parkinson medication
budipine	N04BX03	anti-parkinson medication
opicapone	N04BX04	anti-parkinson medication
levodopa	N04BA01	anti-parkinson medication
levodopa and decarboxylase inhibitor	N04BA02	anti-parkinson medication
levodopa, decarboxylase inhibitor and COMT inhibitor	N04BA03	anti-parkinson medication
melevodopa	N04BA04	anti-parkinson medication
melevodopa and decarboxylase inhibitor	N04BA05	anti-parkinson medication
etilevodopa and decarboxylase inhibitor	N04BA06	anti-parkinson medication
fludrocortisone	H02AA02	Autonomic dysfunction medication
etilefrine	C01CA01	Autonomic dysfunction medication
etilefrine	C01CA01	Autonomic dysfunction medication

Name	ATC code	Category
isoprenaline	C01CA02	Autonomic dysfunction medication
isoprenaline	C01CA02	Autonomic dysfunction medication
norepinephrine	C01CA03	Autonomic dysfunction medication
dopamine	C01CA04	Autonomic dysfunction medication
norfenefrine	C01CA05	Autonomic dysfunction medication
phenylephrine	C01CA06	Autonomic dysfunction medication
dobutamine	C01CA07	Autonomic dysfunction medication
oxedrine	C01CA08	Autonomic dysfunction medication
oxedrine	C01CA08	Autonomic dysfunction medication
metaraminol	C01CA09	Autonomic dysfunction medication
methoxamine	C01CA10	Autonomic dysfunction medication
mephentermine	C01CA11	Autonomic dysfunction medication
dimetofrine	C01CA12	Autonomic dysfunction medication
prenalterol	C01CA13	Autonomic dysfunction medication
dopexamine	C01CA14	Autonomic dysfunction medication
gepefrine	C01CA15	Autonomic dysfunction medication
ibopamine	C01CA16	Autonomic dysfunction medication
midodrine	C01CA17	Autonomic dysfunction medication
octopamine	C01CA18	Autonomic dysfunction medication
fenoldopam	C01CA19	Autonomic dysfunction medication
cafedrine	C01CA21	Autonomic dysfunction medication
arbutamine	C01CA22	Autonomic dysfunction medication
theodrenaline	C01CA23	Autonomic dysfunction medication
epinephrine	C01CA24	Autonomic dysfunction medication
amezinium metilsulfate	C01CA25	Autonomic dysfunction medication
ephedrine	C01CA26	Autonomic dysfunction medication
droxidopa	C01CA27	Autonomic dysfunction medication
combinations	C01CA30	Autonomic dysfunction medication
etilefrine, combinations	C01CA51	Autonomic dysfunction medication
emepronium	G04BD01	Autonomic dysfunction medication
emepronium	G04BD01	Autonomic dysfunction medication
flavoxate	G04BD02	Autonomic dysfunction medication
meladrazine	G04BD03	Autonomic dysfunction medication
oxybutynin	G04BD04	Autonomic dysfunction medication
oxybutynin	G04BD04	Autonomic dysfunction medication
terodiline	G04BD05	Autonomic dysfunction medication
propiverine	G04BD06	Autonomic dysfunction medication
tolterodine	G04BD07	Autonomic dysfunction medication
solifenacin	G04BD08	Autonomic dysfunction medication
trospium	G04BD09	Autonomic dysfunction medication
darifenacin	G04BD10	Autonomic dysfunction medication
fesoterodine	G04BD11	Autonomic dysfunction medication
mirabegron	G04BD12	Autonomic dysfunction medication

Name	ATC code	Category
desfesoterodine	G04BD13	Autonomic dysfunction medication
octreotide	H01CB02	Autonomic dysfunction medication
vasopressin (argipressin)	H01BA01	Autonomic dysfunction medication
desmopressin	H01BA02	Autonomic dysfunction medication
desmopressin	H01BA02	Autonomic dysfunction medication
desmopressin	H01BA02	Autonomic dysfunction medication
desmopressin	H01BA02	Autonomic dysfunction medication
lypressin	H01BA03	Autonomic dysfunction medication
lypressin	H01BA03	Autonomic dysfunction medication
terlipressin	H01BA04	Autonomic dysfunction medication
ornipressin	H01BA05	Autonomic dysfunction medication