Clinical Study Protocol

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

Study No.:	18331A (AMULET – Delay Multiple System Atrophy)
IND No.:	147370
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Edition No.:	6.0
Date of edition:	29 May 2024

Major Changes Since Last Edition

The following summarizes the major changes from Protocol Edition No. 5.0 to 6.0

Chapter/ Section Number	Chapter/Section Title	Change
Throughout the protocol, where applicable		Minor grammatical, editorial, and/or administrative changes have been made to improve the readability and/or clarity of the protocol.
Synopsis	Panel 1	*Added:* The extension of the OLE period was added to the study design figure.
Synopsis	Panel 3	*Added:* The table was updated to include visits from Week 48E onwards.
Synopsis, Section 3.1	Study Methodology, Overview of the Study Design	*Updated:* • 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~~ *166* to ~~142~~ *190* weeks for patients continuing in the OLE. • The individual DBP 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 visit at Week 72 at the time of Last Patient reaches End of Treatment (EoT)~~ *The remaining patients in the DBP will have* their next *scheduled* visit converted to an EoTDBP Visit with assessments as listed for Visit 24, according to Panel 2. • ~~After~~*In the* ~~EoTDBP/End of Open-Label Treatment/~~*OLE, patients will receive Lu AF82422 until Visit 24E (Week 92E) and complete the EoTOLE at Visit 25E (Week 96E).* • Patients who withdraw, except for those who withdraw their consent, will be scheduled for a Withdrawal Visit to undergo clinical and safety assessments as soon as possible~~ and a Safety Follow-up Visit 20 weeks after last dose of IMP.~~ • *All* patients (except the ones withdrawing consent) will be scheduled for a Safety Follow-up Visit 20 weeks after *their* last IMP dose*, regardless if they received their last dose in the DBP or OLE, or if they withdrew.*
Synopsis, Section 3.1,	Study Methodology, Panel 3, Overview of the Study Design	*Added:* *Visit 13E should occur at Week 48E, 4 weeks after Visit 12E. However, in the exceptional cases where sites have not yet received Institutional Review Board/Ethics Committee approval for Protocol Edition 6.0, Visit 13E can be delayed until approval is in place but no later than 5 months after Visit 12E.*

Chapter/ Section Number	Chapter/Section Title	Change
Synopsis, Section 3.1, Section 8.1	Study Methodology, Overview of the Study Design, Overview	*Updated:* The study includes the following periods: • Screening Period (4 weeks) • Randomization Period (2 weeks) • DBP (48 weeks up to 72 weeks) • Optional OLE (*96* weeks) • Safety Follow-up Period (20 weeks after last investigational medicinal product [IMP] administration)
Synopsis, Section 3.1, Section 6.2	Study Methodology, Overview of the Study Design, IMP(s), Formulation(s), and Strength(s)	*Updated:* 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 *from the end of the saline flush* or until stable, whichever is later *(only applicable through Visit 12E). Beginning at Visit 13E, blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes).*
Synopsis, Section 9.6.3	Panel 3, Vital Signs	*Updated:* Blood pressure and pulse will be measured immediately prior to IMP administration and patients will be monitored *immediately* after IMP administration *inclusive of saline flush (±5 minutes)* for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes (±5 minutes) *from the end of the saline flush* or until stable, whichever is later *(applicable only through Visit 12E)*. *Added:* *Beginning at Visit 13E, blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes).*
Synopsis, Section 16.9.7	Statistical Methods, Analysis of Secondary Endpoints(s)	*Updated:* In addition, an exploratory MMRM will be applied to the changes from the ~~original~~ DBP baseline visit ~~to the extract time specific estimates, which will be presented graphically~~. No formal testing will be applied. *Updated:* In addition, an exploratory MMRM as described above will be applied to the changes from the ~~original~~ DBP baseline visit ~~to extract time-specific estimates which will be presented graphically~~. No formal testing will be applied.
Section 3.1	Overview of the Study Design	*Removed:* ~~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 hereafter, 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.~~
Section 3.1	Overview of the Study Design	*Updated:* The study design is presented in Panel 1 and the scheduled study procedures and assessments *for the DBP* are summarized in Panel 2 *and for OLE assessments are summarized in Panel 3*.

Chapter/ Section Number	Chapter/Section Title	Change
Section 3.2	Rationale for the Study Design	*Updated:* The treatment duration of 48 to 72 weeks for patients not entering the optional OLE periods, between ~~118 to 142~~ *166 to 190* weeks for patients continuing in the OLE, is considered a reasonable time window to investigate the natural progression of disease. Since there are currently no available treatments for MSA, Lundbeck wishes to offer patients to continue with, or for patients initially receiving placebo, to receive Lu AF82422 for ~~48~~ *up to 96* weeks in the optional OLE.
Section 5.4	Withdrawal Criteria	*Added:* *The patient can no longer attend trial visits due to MSA disease progression.*
Section 6.1.2	Treatment Regimen Open-label Extension Periods	*Updated:* ~~All~~ *In the OLE, all* patients will receive open-label treatment with Lu AF82422 starting at Visit 1E until Visit ~~12~~ *24*E (Week ~~44~~ *92E*) (see Panel 3). *During the OLE period, any* deviation from the Q4W ±3 days dosing schedule must be discussed and agreed with the medical monitor and documented as a protocol deviation. IMP dosing must not take place if less than 2 weeks until the next scheduled IMP infusion. After Visit ~~13~~ *25*E, or if prematurely discontinued, patients will be scheduled for a Safety Follow-up Visit 20 weeks after the last IMP dose, as scheduled in Panel 3.
Section 3.1, Section 8.5	Overview of the Study Design, Optional Open-label Extension Period	*Updated:* If a Safety Follow-up Visit for the DBP is due before the OLE is implemented, it should be completed per Panel 2. The patient could afterwards enter the OLE and treatment could continue for a planned period of ~~48~~ *96* weeks.
Section 8.5.1	End-of-Treatment Visit – Optional Open-label Extension Periods	*Updated:* Patients who enter the OLE will receive the first open-label dose of Lu AF82422 (Visit 1E) on the same day as the EoTDBP or as soon as possible thereafter and the last *dose* on Visit ~~12E~~ *24E* (Week ~~44),~~ *92E*); EoT in the ~~48~~ *96*-week OLE is ~~on 13E~~ *at Visit 25E* (Week ~~48~~ *96E*).
Section 8.6	Withdrawal Visit	*Updated:* Patients who withdraw from the study prior to the *respective* EoT Visit *for the treatment period (ie, EoTDBP or EoTOLE)* will be asked to attend a Withdrawal Visit and Safety Follow-up Visit, if at all possible.
Section 9.2.1.5	Clinical Global Impression-Severity of Illness (CGI-S)	*Updated:* 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~~ *at the time of assessment.*

Chapter/ Section Number	Chapter/Section Title	Change
Section 9.6.2	Panel 5	*Updated:* Count and % of total leucocytes. *If any abnormalities are noted in the complete blood count and/or differential counts, additional workup (ancillary tests) will be performed.*
Section 9.8.2, Section 9.8.3, Section 9.8.4, Section 9.8.5	Blood Sampling for Gene Expression Profiling (RNA), Blood Sampling for Metabolomics and/or Proteomics, Blood Sampling for Pharmacogenetics, Blood Sampling for Anti-drug Antibody	*Updated:* ~~Brooks~~ *Azenta* Life Sciences, Indianapolis, IN, US
Section 10.2	Pregnancy	*Updated:* The investigator must follow-up on the *outcome* of the pregnancy and report it on a Pregnancy *Outcome* Form (paper). The follow-up must include information on the neonate at least up until the age of 1 month. If the partner of a man participating in the study becomes pregnant, the *pregnancy should be reported on the Pregnancy Reporting Form (paper) and the outcome* of the pregnancy should be followed *and reported (Pregnancy Outcome Form)* if the partner agrees. The partner must sign a pregnant partner *Informed Consent Form* to allow the investigator to collect information to report to Lundbeck.

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

ADA	anti-drug antibodies
AE	adverse event
ALT	alanine aminotransferase
APRS	all-patients-randomized set
APTS	all-patients-treated set
APTS-FU	all-patients-treated set follow-up
ARDS	acute respiratory distress syndrome
ASL	arterial spin labelling
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
aUMSARS	abbreviated Unified Multiple System Atrophy Rating Scale
BL	baseline
BMI	body mass index
Bpm	beats per minute
CBF	cerebral blood flow
CGI-S	Clinical Global Impression – Severity
CNS	central nervous system
CNVs	copy number variations
COA	clinical outcome assessment
COMPASS S	Composite Autonomic Symptom Scale Select score
COMPASS SC	Composite Autonomic Symptom Scale Select Change score
COVID-19	coronavirus disease 2019
CRA	clinical research associate
CRO	clinical research organization
CRS	Cytokine Release Syndrome
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	Double-blind Period
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DTI	diffusion-tensor imaging
EC	ethics committee
ECG	electrocardiogram
eCOA	electronic COA
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid

EIS	Exit Interview subset
EMSA	European Multiple System Atrophy Registry
EOI	end of infusion
EoT	end-of-treatment
EoTDBP	end-of-treatment of Double-blind Period
EoTOLE	end-of-treatment of the Open-label Extension Period
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-dimension, 5-level
EU	European Union
FAS	full-analysis set
FDA	Food and Drug Administration (United States)
FDG	fluorodeoxyglucose
FIH	first-in-human
GCI	glial cytoplasmic inclusions
GMP	Good Manufacturing Practice
GRE	gradient-recalled echo
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iDMC	Independent Data Monitoring Committee
IEs	intercurrent events
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
IV	Intravenously
LEDD	levodopa equivalent daily dose
Lu	Lundbeck
mAb	monoclonal antibody
MAO-B	monoamine oxidase B
MCID	minimal clinically important difference
MM-QAP	Mixed Methods Qualitative Analysis Plan
MMRM	mixed model for repeated measurements
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging

mRNA	messenger ribonucleic acid
MSA	multiple system atrophy
MSA-C	multiple system atrophy cerebellar type
MSA-P	multiple system atrophy parkinsonian type
mUMSARS	modified Unified Multiple System Atrophy Rating Scale
NfL	neurofilament light chain
NOAEL	no observed adverse effect level
OGI-S	Observer-reported Global Impression - Severity of Illness
OLE	Open-label Extension
OLES	Open-label Treatment Extension Set
PAE	potential adverse events
PCR	polymerase chain reaction
PCS	potentially clinically significant
PD	Progressive disease
PET	positron emission tomography
PGI-S	Patient Global Impression – Severity
PK	pharmacokinetic(s)
PKS	PK set
PR	specific ECG interval describing atrioventricular conduction
PRO	patient-reported outcome
Q4W	every 4 weeks
QAP	Qualitative Analysis Plan
QP	qualified person
qPCR	quantitative polymerase chain reaction
QRS	specific ECG interval describing ventricular depolarization
QT	specific ECG interval describing ventricular depolarization/repolarization
QT_c	heart rate corrected QT interval
QT_{cF}	heart rate corrected QT interval using Fridericia's correction formula
RCT	randomized controlled trial
RNA	ribonucleic acid (micro [miRNA], circular [circRNA] RNA)
ROI	regions-of-interest
RR	specific ECG interval describing the ventricular depolarization/repolarization cycle
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	statistical software package from the SAS® Institute
SBS	Sensor-based subset
SE-ADL	Schwab and England Activities of Daily Living scale
SEIS	Study Experience Interview subset
SFU-E	Safety Follow-up Extension

SNP	single nucleotide polymorphism
SOC	standard of care
$t_{½}$	apparent elimination half-life
TE	target engagement
TEAE	treatment-emergent adverse event
TMF	trial master file
UMSARS	Unified Multiple System Atrophy Rating Scale
UMSARS TS	Unified Multiple System Atrophy Rating Scale Total Score
US	United States
VAS	visual analogue scale
vMRI	volumetric MRI

1 Synopsis – Study 18331A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Lu AF82422
Study 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	
Objectives and Endpoints	
Objectives	**Endpoints**

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)
	Disease progression
	• Primary endpoint:
	  • 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 End-of-Treatment of the DBP (EoTDBP)
	• Key secondary endpoint:
	  • Disease progression, as assessed by longitudinal changes from baseline in modified UMSARS Part I (mUMSARS) score up to EoTDBP
	• Secondary endpoints:
	  • Disease progression, as assessed by longitudinal changes from baseline in the UMSARS Part I and UMSARS Part II scores up to EoTDBP
	  • Change from baseline up to Week 48 in the DBP in UMSARS TS, UMSARS Part I, mUMSARS and UMSARS Part II scores
	• Exploratory endpoint:
	  • Disease progression, as assessed by longitudinal changes from baseline in the abbreviated UMSARS (aUMSARS) up to EoTDBP

Secondary Objectives
• To evaluate the efficacy of Lu AF82422 on:
  • Function
  • Global impression, severity of illness during the DBP
	Function
	• Secondary endpoint:
	  • Change from baseline to Week 48 in the DBP in Schwab and England Activities of Daily Living (SE-ADL) score
	Global impression
	• Secondary endpoints:
	  • Change from baseline to Week 48 in the DBP in Clinical Global Impression – Severity of Illness (CGI-S) score
	  • Change from baseline to Week 48 in the DBP in Patient Global Impression – Severity of Illness (PGI-S) score
	  • Change from baseline to Week 48 in the DBP in Observer-reported Global Impression – Severity of Illness (OGI-S) score

Secondary Objectives (continued)	Endpoints (continued)

• To evaluate the efficacy of Lu AF82422 on:
  • Autonomic symptoms
  • Global disability
  • Disease milestones
  • Health-related quality of life during the DBP
	Autonomic symptoms
	• Secondary endpoint:
	  • Change from baseline to Week 48 in the DBP in Composite Autonomic Symptom Score Select Change (COMPASS Select Change) score
	• Exploratory endpoint:
	  • Change from baseline to Week 48 in the DBP in heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III
	
	Global disability
	• Secondary endpoint:
	  • Change from baseline to Week 48 in the DBP in UMSARS Part IV score
	
	Disease milestones
	• Secondary endpoints:
	  • Change from baseline to Week 48 in the DBP in speech, swallowing, falls and walking, as assessed by the UMSARS Part I item scores
	  • Change from baseline to Week 48 in the DBP in frequency, cause and consequence of falls, as assessed by the fall diary periods
	• Exploratory endpoints:
	  • Time to wheelchair use
	  • Change from baseline to Week 48 in the DBP in frequency of falls, as assessed by PAMSys (subset)
	  • Change from baseline to Week 48 in the DBP in gait parameters, as assessed by FeetMe® (subset)
	
	Health-related quality of life
	• Secondary endpoint:
	  • Change from baseline to Week 48 in the DBP in EuroQol 5-dimension, 5-level (EQ-5D-5L) score

• To evaluate the efficacy of Lu AF82422 on disease progression, as measured by brain Magnetic Resonance Imaging (MRI)	**MRI biomarkers** • Secondary endpoint: • Percentage change from baseline to Week 48 in the DBP 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)

Secondary Objectives (continued)	Endpoints (continued)

	• Exploratory endpoints:
	  • Percentage change from baseline to Week 48 in the DBP 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
	  • Percent change from baseline to Week 48 in the DBP in cerebral blood flow (CBF) in ROIs; putamen and cerebellum, as measured by arterial spin labelling (ASL) MRI

• To evaluate the efficacy of Lu AF82422 on biofluid biomarkers of disease progression during the DBP	**Biofluid biomarkers**
	• Secondary endpoint:
	  • Blood biomarkers: Change from baseline up to Week 48 in the DBP in neurofilament light chain (NfL) concentrations
	• Exploratory endpoints:
	  • Cerebrospinal fluid (CSF) biomarkers: Change from baseline up to Week 48 in the DBP in t-tau and NfL concentrations

• To evaluate the pharmacokinetics of Lu AF82422	**Pharmacokinetics**
	• Secondary endpoints:
	  • Lu AF82422 plasma concentration during treatment and Safety Follow-up
	  • Lu AF82422 CSF concentrations and the CSF/plasma concentration ratios at Week 48 in the DBP

Exploratory Objectives	Endpoints (Exploratory)

To explore the target engagement (TE) of Lu AF82422 to α-synuclein during the DBP	• Blood:
	  • Plasma concentrations of "free" and "total" α-synuclein during treatment and Safety Follow-up
	• CSF:
	  • Concentrations of "free" and "total" α-synuclein at baseline and Week 48 in the DBP

To explore the TE of Lu AF82422 to pathological species of α-synuclein during the DBP	• CSF biomarkers: • Changes from baseline up to Week 48 in the DBP in pathological species of α-synuclein

To explore the relationship between UMSARS, MRI parameters and NfL during the DBP	• Relationship between:
	  • Change from baseline to Week 48 in the DBP in UMSARS TS, Part I and Part II scores,
	  • Percentage change from baseline to Week 48 in the DBP in brain volume and tissue integrity in brain ROIs as measured by MRI, and
	  • Change from baseline up to Week 48 in the DBP in NfL concentrations.

• To explore the effect of long-term treatment with Lu AF82422 during the open-label extension (OLE)	• Effect of 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 EuroQol 5-dimension, 5-level (EQ-5D-5L) score
	  • Percentage change from baseline of the DBP and baseline of the OLE to 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

Exploratory Objectives	Endpoints (Exploratory)

• To explore the efficacy of Lu AF82422 for up to 72 weeks of treatment on clinical scales and biomarkers during the DBP	• Clinical scales:
	  • Change from baseline to EoTDBP in UMSARS Part I items 1, 2, 7 and 8, Part III and Part IV, and SE-ADL, CGI-S, PGI-S, OGI-S, COMPASS Select Change and EQ-5D-5L scores
	• Blood biomarkers:
	  • Change from baseline to EoTDBP in NfL concentrations
	• MRI biomarkers:
	  • Change from baseline to EoTDBP in vMRI, DTI and ASL measures

• To collect patient experience with impaired functions due to MSA to support the interpretation of change during the study (Exit Interview subset) during the DBP	• Describe patient experience data and meaningful change (for example, symptoms, function, quality of life and disease manifestations) from the patient's and caregiver's perspective, as assessed by the Exit interviews
• To collect patient experience with study participation (Study Experience Interview subset) during the DBP	• Describe patient experience data (for example, study experience, operational considerations, satisfaction with study experience, suggestions) from the patient's and caregiver's perspective, as assessed by the Study Experience interviews
Safety Objective	**Safety Endpoints**

• To evaluate the safety and tolerability of Lu AF82422 in patients with MSA in the DBP	Double-blind Period
	  • Treatment-emergent adverse events
	  • Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and electrocardiogram (ECG) parameter values
	  • Development of specific anti-drug antibodies (ADAs)
	  • Findings on MRI during the DBP, as specified in the *Imaging Charter*
	  • Columbia-Suicide Severity Rating Scale (C-SSRS) score

• To evaluate safety and tolerability of Lu AF82422 in patients with MSA in the Open-label Extension Period	Open-label Extension
	  • 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 ADAs
	  • C-SSRS score

Study Methodology

- This is a phase II, interventional, randomized, double-blind, parallel-group, placebo-controlled, including an optional open-label extension (OLE), 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 current consensus 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 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 and Region (United States [US]/Japan, with a maximum of 25% of patients from Japan). All patients entering the OLE will receive Lu AF82422 CCI during the OLE.
- 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 166 to 190 weeks for patients continuing in the OLE.
- The study includes the following periods:
  - Screening Period (4 weeks)
  - Randomization Period (2 weeks)
  - DBP (48 weeks up to 72 weeks)
  - Optional OLE treatment period (96 weeks)
  - Safety Follow-up Period (20 weeks after last investigational medicinal product [IMP] administration)
- Patients who do not consent to the optional OLE will enter the Safety Follow-up Period after the EoTDBP Visit.
- The individual DBP 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. The remaining patients in the DBP will have their next scheduled visit converted to an EoTDBP Visit with assessments as listed for Visit 24, according to Panel 2. During the DBP, patients will attend IMP Visits to follow a dosing schedule with either Lu AF82422 or placebo every 4 weeks (Q4W).
- Patients who enter the OLE will receive the first open-label dose (Visit 1E) on the same day as the EoTDBP or as soon as possible thereafter, but no later than 5 months after the EoTDBP Visit and will be enrolled to OLE no later than the end of Q1 2024.
- In the OLE, patients will receive Lu AF82422 until Visit 24E (Week 92E) and complete the EoTOLE at Visit 25E (Week 96E). Visit 13E should occur at Week 48E, 4 weeks after Visit 12E. However, in the exceptional cases where sites have not yet received Institutional Review Board/Ethics Committee approval for Protocol Edition 6.0, Visit 13E can be delayed until approval is in place but no later than 5 months after Visit 12E.
- Patients who withdraw, except for those who withdraw their consent, will be scheduled for a Withdrawal Visit to undergo clinical and safety assessments as soon as possible.
- All patients (except the ones withdrawing consent) will be scheduled for a Safety Follow-up Visit 20 weeks after their last IMP dose, regardless if they received their last dose in the DBP or OLE, or if they withdrew.
- 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 from the end of the saline flush or until stable, whichever is later (only applicable through Visit 12E). Beginning at Visit 13E, blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes).
- CSF assessments for evaluation of pharmacokinetics (PK), TE, and biomarkers at baseline and after initiation of treatment will be collected according to Panel 2. CSF sampling is 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

Study Methodology (continued)

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.

- Patients must visit designated imaging facilities for MRI scans for eligibility, safety and efficacy. The presence of MRI abnormalities supporting the diagnosis of MSA will also be recorded. The scans will be evaluated by a central reader, as pre-specified in the study-specific *Imaging Charter*.

  At all the US sites, additional assessments (objective sensor-based assessments and qualitative Exit interviews) will be performed (hereafter referred to as the "Sensor subset" and "Exit Interview subset"). Participation in the Exit Interview subset is mandatory for patients and caregivers, while participation in the Sensor subset is optional. Patients who wish to participate in the Sensor subset must provide specific consent to one or both devices as part of the main *Informed Consent Form*. Patients can withdraw from these additional assessments without having to withdraw from the main study. Additionally, at US sites, a subset of patients and caregivers may be contacted about an opportunity to participate in a Study Experience interview ("Study Experience Interview subset").
- An independent Data Monitoring Committee (iDMC) will regularly monitor the patients' safety data according to the *Data Monitoring Committee (DMC) Charter* during the DBP**.**
- The study design is presented in Panel 1 and the scheduled study procedures and assessments for DBP are summarized in Panel 2 and for OLE assessments are summarized in Panel 3.

Number of Patients Planned

60 patients, recruited from specialist centres, are planned for randomization: 40 in the Lu AF82422 CCI group and 20 in the placebo group.

Target Patient Population

Main Inclusion Criteria

- Diagnosis of possible or probable MSA-P or MSA-C according to the *Gilman criteria* at the Screening Visit
- Less than 5 years from the time of onset of motor MSA symptoms at the Screening Visit in the judgement of the investigator
- Anticipated survival of at least 3 years, in the opinion of the investigator, at the Screening Visit
- An UMSARS Part I score ≤16 (omitting item 11 on sexual function) at the Screening Visit
- Cognitive performance evaluated by the Montreal Cognitive Assessment (MoCA) with a score ≥22 at the Screening Visit
- The patient has a knowledgeable and reliable caregiver who will be available throughout the study when carer/observer-reported outcomes are performed. A caregiver is defined as a person who spends approximately 3 hours or more with the patient per week and can inform on level of function of the patient.
- Aged ≥40 and ≤75 years at the Screening Visit

Open-label Extension Entry Criteria

- The patient has completed the EoTDBP Visit and did not withdraw in the DBP
- The patient has consented to participate in the OLE
- The patient has completed the EoTDBP within the last 5 months and will be enrolled into the OLE no later than end of Q1 2024
- The patient is, in the investigator's opinion, likely to comply with the protocol
- The patient has not received any other investigational product since the EoTDBP Visit

Main Exclusion Criteria

- Treatment with an anti-α-synuclein monoclonal antibody (mAb) or an inhibitor of α-synuclein aggregation within the last 12 months
- Any past or current treatment with an active vaccine targeting α-synuclein
- The patient has two or more blood relatives with a history of MSA
- Evidence (clinically or on MRI) and/or history of any serious neurological disorder, other intracranial or systemic diseases or conditions resulting in a diagnosis other than MSA
- Current diagnosis of movement disorders that could mimic MSA; for example, Parkinson's disease, dementia

Target Patient Population (continued)

Main Exclusion Criteria (continued)

with Lewy bodies, essential tremor, progressive supranuclear palsy, spinocerebellar ataxia, spastic paraparesis, corticobasal degeneration, or vascular, pharmacological or post-encephalitic parkinsonism, per investigator discretion. Patients who have previously been diagnosed with Parkinson's disease will not be excluded

- History of severe drug allergy, anaphylaxis or hypersensitivity or known hypersensitivity or intolerance to the IMP or its excipients
- History of neurosurgical procedures including deep brain stimulation that could, in the investigator's opinion, interfere with the assessments of safety or efficacy
- Contraindications for MRI
- Attempted suicide within the past 6 months or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS within the past 6 months)
- The following recent and concomitant medications are disallowed or allowed with restrictions with respect to their use prior to or during the study (the list is not comprehensive):
  - *Disallowed*: any investigational products within 30 days before the Screening Visit, treatment targeting α-synuclein and/or MSA disease progression
  - *Allowed with restriction*: stable dose for at least 8 weeks prior to randomization of drugs acting against parkinsonism (for example Levodopa, Dopamine-Agonists, Amantadine and Monoamine oxidase b [MAO-B] inhibitors) and/or drugs acting against autonomic dysfunction (for example, ephedrine, droxidopa, midodrine, fludrocortisone, octreotide, desmopressin, oxybutynin) and anticipated stable during the DBP. If medically necessary, initiation of or change of dose of concomitant medication is allowed per investigator discretion.

Investigational Medicinal Product, Doses and Modes of Administration

Lu AF82422 is a human recombinant monoclonal antibody of the immunoglobulin G1 (IgG1) isotype that recognizes all major species of α-synuclein (oligomer and fibrillar forms; N- or C-terminal truncated forms). Lu AF82422 targets extracellular α-synuclein and inhibits seeding and spreading of pathological form(s) of α-synuclein in *in vitro* and *in vivo* models.

Dosage form:

- Lu AF82422 solution for infusion 53 mg/mL, dose CCI
- Placebo to Lu AF82422 solution for infusion

Route of administration: intravenous infusion over 30 minutes (±10 minutes) once every 4 weeks.

Assessment Details/Biomarker Methodology

The assessments are summarized in Panel 2 and Panel 3. Details for selected assessments are provided below.

Blood and CSF assessments will be conducted using validated bioanalytical methods as specified in the *Laboratory Specification Manual*. Imaging assessments will be conducted according to the study-specific *Imaging Manual*. The scans will be evaluated by a central reader as pre-specified in the study-specific *Imaging Charter*.

Efficacy Assessments

- The UMSARS is a combined clinician and patient/caregiver-reported scale to assess disease progression in patients with MSA. The mUMSARS score will consist of UMSARS Part 1 where the response option scores of 0 and 1 will be collapsed to one category in the analysis. The aUMSARS score is derived from a subset of items from UMSARS Part I and Part II shown to be patient centric and sensitive to progression in MSA. Thus, the UMSARS will be administered only once to the patient (according to standard procedures) at the clinic visit to derive the UMSARS TS, mUMSARS and aUMSARS scores. The administration of UMSARS Part I and Part II will be video recorded for central reading.
- The COMPASS Select Change is derived from the original COMPASS scale applying a computerized algorithm. Data will be submitted to Mayo Clinic for calculations.
- MRI scan for evaluation of biomarkers of disease progression:

Assessment Details/Biomarker Methodology (continued)
Efficacy Assessments (continued)

- vMRI for quantification of atrophy measures in brain ROIs; primary ROIs: pons and cerebellum; secondary ROIs: caudate nucleus, putamen, brain stem and total grey matter
- DTI in the DBP for quantification of diffusivity measures in brain ROIs; primary ROIs: putamen, cerebellar cortex and white matter; secondary ROIs: caudate nucleus, globus pallidus and middle cerebellar peduncle
- ASL in the DBP for quantification of CBF in selected brain regions (for example, putamen and cerebellum)

- Blood sampling for biomarkers of disease progression; for quantification of NfL
- CSF sampling for biomarkers of disease progression; for quantification of t-tau and NfL
- Fall diary; assessment of Date/Time of fall; Context of fall; Causes of the fall; Consequences of the fall. Patients will receive diary training at the Randomization Visit and then start the diary data entries.
- FeetMe® sensor-based device; consists of a pair of digital insoles to be placed in patients' shoes for remote and continuous assessment of gait, which will be self-administered in the remote environment (Sensor subset).
- PAMSys sensor-based device; consists of a wearable sensor worn as a pendant on the chest and an electronic diary for a remote monitoring of falls and mobility, which will be self-administered in the remote environment (Sensor subset).
  - Data from the fall diary and the Sensor subset will be collected during the Randomization period, and then for four pre-defined periods during the study according to Panel 2. The fall diary and devices will be handed out and returned at standard in-clinic visits. 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 and the sensors are to be dispensed.

Pharmacokinetic Assessments

- Blood sampling; for quantification of "free" (that is, not bound to α-synuclein) Lu AF82422 in plasma
- CSF sampling; for quantification of "free" (that is, not bound to α-synuclein) Lu AF82422 in CSF

Target Engagement Assessments

- Blood sampling for α-synuclein; for quantification of "free" and "total" α-synuclein in plasma
- CSF sampling for α-synuclein; for quantification of "free" and "total" α-synuclein
- CSF sampling for pathological species of α-synuclein (for example, aggregated and truncated species)

Safety Assessments

- MRI for safety during the DBP; for evaluation of clinically important findings for example, oedema, microhaemorrhages, infarcts and meningoencephalitis
- Blood Sampling for ADA analysis; plasma samples to determine presence or absence of ADAs. Samples confirmed positive for ADA will be evaluated for clearing ADAs by evaluation of exposure and TE.
- Adverse events requiring additional data collection: hypersensitivity reactions

Assessment Details/Biomarker Methodology (continued)

Other Study Procedures and Assessments

Qualitative semi-structured Exit interviews will be conducted via telephone or web conferencing platform (for example, Microsoft Teams) in patients and caregivers from the US sites (Exit Interview subset). The Exit interviews will take place approximately 3 weeks after the EoTDBP Visit or Withdrawal Visit. For patients withdrawing from the study, the Exit interview will only be performed if they have been in the DBP for at least 48 weeks. The interviews are tailored to the MSA population and this study in order to describe patient experience data and meaningful change (for example, symptoms, function, quality of life and disease manifestations) from the patient's and caregiver's perspective to support the interpretation of change during the study. The interviews will follow a separate interview protocol and will be conducted by ICON.

Additionally, a subset of patients and caregivers at US sites may be contacted to participate in a second semi-structured interview focused on Study Experience ("Study Experience Interview subset"). The interview will include topics such as logistical considerations, satisfaction with study experience, and suggestions for improvement for future studies. The interviews will follow a separate interview protocol and will be conducted by web conferencing service (for example, Microsoft Teams) or telephone by trained interviewers from ICON. The Study Experience interview will take place after completion of the Exit interview, no later than 6 weeks after the Exit interview.

Statistical Methodology

- 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 received at least one dose of double-blind IMP
  - *all-patients-treated-follow-up set* (APTS-FU) – all patients in the APTS who complete the DBP and who has data collected up to or at the Safety Follow-up DBP visit
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of UMSARS Part I and Part II prior to or at withdrawal from treatment in the DBP
  - *PK subset* (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
  - *exit interview subset* (EIS) – all patients in the FAS having a complete Exit interview with the patient and/or the caregiver
  - *study experience interview subset* (SEIS) – 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
- Since the primary, key secondary and selected secondary analyses on the UMSARS scores will be performed in a Bayesian framework, the success thresholds for the Bayesian posterior probability of superiority relative to placebo will be calibrated through simulations to correspond to a significance level of 5% evaluated one-sided. For the frequentist analyses, the significance level will be 5%, which will be applied one-sided. A testing strategy will be implemented including UMSARS TS and mUMSARS to protect the type I error for these two endpoints.
- The study primary estimand will be:
  - CCI [redacted]

Statistical Methodology (continued)

- CCI [redacted]

- Primary analysis: The primary efficacy analysis, that is, estimator, following up to 72 weeks of treatment will be based on the FAS and a Bayesian repeated measures model of the change from baseline in the UMSARS TS. The repeated measures model incorporates the following features:
  - Fixed effects for change in UMSARS progression per visit
  - Participant-level random effects for the rate of UMSARS progression across visits
  - Fixed multiplicative treatment effect, θ, for increase or decrease in the overall rate of UMSARS progression of Lu AF82422 relative to placebo common across all visits. In particular, if $\theta<1$, the active treatment slows the rate of progression of UMSARS relative to placebo. If $\theta>1$, the active treatment increases the rate of progression of UMSARS relative to placebo. If $\theta = 1$, the rate of progression of UMSARS 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 for CCI [redacted] and region (US and Japan) common across all visits
  - Prior distribution for model parameters selected in a conservative and non-informative manner using relatively large outcome spaces
  - Sensitivity analyses to cover model assumptions and handling of missing data applying different imputation strategies
- Analysis of the key secondary, secondary and exploratory endpoints in the DBP:
  - All secondary and exploratory analyses will be based on the FAS.
  - For the key secondary endpoint, that is, changes in mUMSARS from baseline up to EoT, a Bayesian repeated measures model will be applied similar to the primary analysis.
  - For changes in UMSARS Part I and UMSARS Part II scores up to EoT, a Bayesian repeated measures model will be applied similar to the primary analysis.
  - All remaining continuous secondary and exploratory endpoints (for example, clinical scales/assessments and MRI parameters) will be analyzed applying a Mixed Model for Repeated Measurements (MMRM) to the changes from baseline up to Week 72. If required, a log transformation will be applied for normalization. Treatment estimates will be derived for each subsequent visit. The primary comparison will be at Week 48, whereas Week 72 will be exploratory.
  - All categorical secondary and exploratory endpoints following 48 weeks and 72 weeks of treatment will be analyzed applying a logistic regression model. Week 48 data will be primary.
  - Number of falls per individual per fall diary period, according to the patient fall diary, will be analyzed applying a negative binomial regression model. A similar model will be applied to the falls collected by the sensor-based PAMSys device, if applicable, including data from the pre-defined periods only.
  - Additional time-to-event secondary and exploratory endpoints following 48 weeks and 72 weeks of treatment will be analyzed applying a Cox proportional-hazards model. Week 48 will be primary.
  - Lu AF82422 plasma concentrations, CSF concentrations, and the CSF/plasma concentration ratios during treatment for all patients will be presented descriptively. The data will be included in a separately reported population pharmacokinetics analysis.
  - Absolute values and changes from baseline up to Week 48 and Week 72 in blood biomarkers and Week 48 in CSF biomarkers will be analyzed descriptively. For selected parameters, a MMRM will be applied for the changes from baseline to EoTDBP. If required, a log transformation will be applied for normalization.

Statistical Methodology (continued)

- TE of Lu AF82422 to α-synuclein in CSF will be presented descriptively as "free" synuclein, "total" α-synuclein and ratio of "free" to "total" α-synuclein.
- The relationship between changes in selected blood/CSF biomarkers, that is, NfL, t-tau and changes in MRI parameters, and changes in main clinical outcome, that is, UMSARS scores, will be explored graphically and using partial correlation coefficients.
- Gait and balance parameters derived from the sensor-based FeetMe® device will primarily be analyzed descriptively for the SBS. If appropriate, a MMRM model, like the one described above for continuous secondary and exploratory endpoints, will be applied. Correlation to the key progression markers, which is the UMSARS scores and MRI parameters, will be explored graphically.
- The potential influence of covariates (in addition to CCI and region) will be investigated using a frequentist repeated measures analysis with fixed effects. Among the covariates to be investigated are age, gender, country, race, time-since-diagnosis, dose of Parkinson's disease medication (expressed as levodopa equivalent daily dose [LEDD]), baseline MRI signal, and baseline plasma/CSF α-synuclein and NfL levels.
- The analysis of semi-structured Exit interviews and Study Experience interviews will be pre-specified in a specific Qualitative Analysis Plan (QAP).

Analysis of OLE efficacy data:

- Analysis of exploratory efficacy data collected in the OLE will be based on the OLES where the original placebo patients will be handled as a separate group.
- All continuous endpoints following treatment extension will primarily be analyzed descriptively. In addition, an exploratory MMRM will be applied to the changes from the DBP baseline visit. No formal testing will be applied. Further details on the model will be outlined in the Statistical Analysis Plan (SAP).

A study-specific SAP will be developed for this study to describe further details on the proposed analyses. In addition, there will be a separate *Psychometric SAP* which will include the description of the methods and analytical principles to preliminarily explore in this study the psychometric properties and the meaningful within-patient change of the UMSARS TS, mUMSARS and aUMSARS.

- Patient disposition and demographics will be summarized using descriptive statistics.
- Reason for withdrawal will be investigated and compared between Lu AF82422 and placebo.
- The use of concomitant medication will be analyzed descriptively.
- Analysis of safety endpoints:
  - The safety analyses will be based on the APTS and the OLES.

Treatment-emergent adverse events, clinical safety laboratory tests, vital signs, weight/body mass index (BMI), ECG parameters, C-SSRS, MRI findings, and presence of ADAs will be summarized using descriptive statistics.

Testing Strategy

A testing strategy will be applied including the primary endpoint, that is, UMSARS TS and the key secondary endpoint, that is, mUMSARS to protect the type I error for these endpoints in a hierarchical manner.

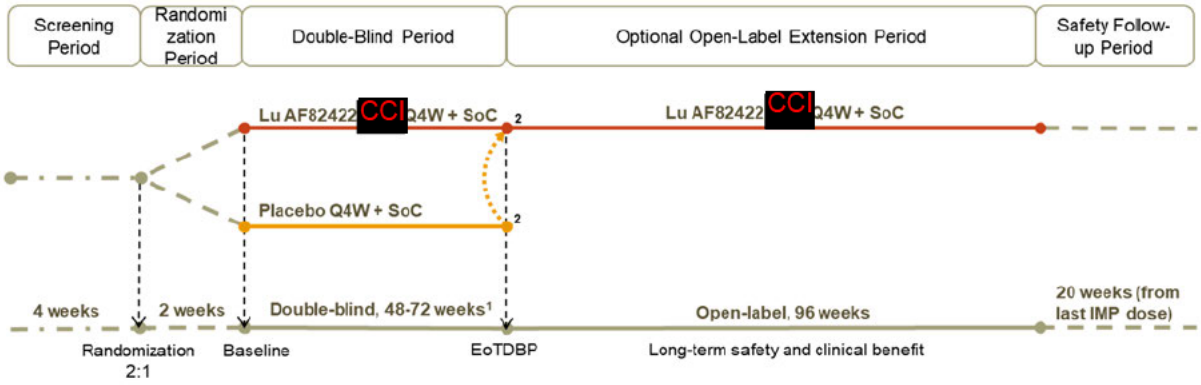
Sample Size Considerations

CCI

CCI

The 18331A sample size has been selected to ensure an appropriate power to detect a 40% slowing in MSA progression in the Lu AF82422CCI dose group compared to the placebo group on a 5% significance level evaluated one-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 (that is, 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 of weeks data and 25% of the patients with full 72 weeks of 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.

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 EoTDBP Visit 4 weeks after latest dose of IMP
2. Patients who do not continue in the optional OLE will enter the Safety Follow-up Period after the EoTDBP Visit

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

Panel 2 Study Procedures and Assessments - Double-blind 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/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	EoTDBP/WD[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 (for example, 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			√						√			√			√			√			√			√	
Fall diary, daily recording		√[g]	√[h]				√[g]		√[h]		√[g]	√[h]		√[g]	√[h]		√[g]	√[h]							
FeetMe® (subset) optional[i]		√[j]	√[k]				√[j]		√[k]		√[j]	√[k]		√[j]	√[k]		√[j]	√[k]							
PAMSys (subset) optional[i]		√[j]	√[k]				√[j]		√[k]		√[j]	√[k]		√[j]	√[k]		√[j]	√[k]							

Visit Name	Screening	Randomization	Baseline + IMP	Telephone Visit	IMP	Site Visit	IMP	Telephone Visit	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	EoTDBP/WD[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**
MRI scan: vMRI, DTI and ASL measures[l,m]			√						√			√						√						√[n]	
CSF sampling[o] for NfL and t-tau			√															√						√[p]	
Blood sampling for NfL	√		√						√			√			√			√						√	
Quality of Life Assessments																									
EQ-5D-5L			√									√						√						√	
Pharmacokinetic Assessments																									
Blood sampling for IMP quantification[q]			√[q]		√	√	√		√[q]			√			√[q]			√			√			√	√
CSF sampling[o] for IMP quantification			√															√						√[p]	
Target Engagement Assessments																									
CSF sampling[o] for α-synuclein and pathological species of α-synuclein			√															√						√[p]	
Blood sampling for α-synuclein[q]			√[q]		√	√	√		√[q]			√			√[q]			√			√			√	√
Safety Assessments																									
AEs			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Follow-up of adverse events on-going at EoTDBP or withdrawal, and new AEs and SAEs																									√
Blood and urine sampling for clinical safety laboratory tests	√		√		√	√	√		√			√			√			√			√			√	√
Blood sampling for ADAs			√		√	√	√		√			√			√			√			√			√	√
Vital signs[r]			√		√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Weight	√		√						√			√			√			√						√	
Examinations (physical, neurological)[s]	√		√		√	√			√			√			√			√						√	
ECG	√		√			√						√						√						√	
MRI scan for safety[m]			√						√			√						√						√[n]	
C-SSRS[t]	√		√		√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Visit Name	Screening	Randomization	Baseline + IMP	Telephone Visit	IMP	Site Visit	IMP	Telephone Visit	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	IMP/EoTDBP[a]	EoTDBP/WD[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)[u]			√									√						√							
Blood sampling for metabolomics/proteomics (plasma)[u]			√									√						√							
Blood sampling for pharmacogenetics (DNA) (optional)[v]			√																						
Blood sampling for ADA			√		√	√	√		√			√			√			√			√			√	√
CSF sampling[o]			√															√						√[p]	
Other Study Procedures and Assessments																									
IMP administration[r]			√		√		√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Concomitant medication (prescription and non-prescription)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test, urine dipstick[w]		√	√		√		√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Exit interview (subset)[x]																								√	

ADA = anti-drug antibody; AE = adverse event; ASL = arterial spin labelling; 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; DBP = Double-blind Period; DNA = deoxyribonucleic acid; DTI = diffusion-tensor imaging; ECG = electrocardiogram; EOI = end of infusion; EoT = End-of-Treatment; EoTDBP = End-of-Treatment DBP; EQ-5D-5L = EuroQol 5-Dimensions, 5-Levels; IMP = investigational medicinal product; IRT = Interactive Response Technology; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; MSA = Multiple System Atrophy; MSA-C = MSA with predominant cerebellar features; MSA-P = MSA with predominant parkinsonism; NfL = neurofilament light chain; OGI-S = Observer-rated Global Impression – Severity of Illness; OLE = Open-label Extension Period; PGI-S = Patient Global Impression – Severity of Illness; PK = pharmacokinetics; RNA = ribonucleid acid; SAE = serious adverse event; SCR = screening; SE-ADL = Schwab & England Activities of Daily Living; SFU = Safety Follow-up of DBP; T-tau = total tau; UMSARS = Unified Multiple System Atrophy Rating Scale; US = United States; vMRI = volumetric magnetic resonance imaging; WD = withdrawal

a. When the last patient randomized reaches Visit 18/Week 48, the remaining patients in the DBP will have their next scheduled visit converted to an EoTDBP 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 Follow-up Visit 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 m); 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 10 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. 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.
j. 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.
k. 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.
l. 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.
m. 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.
n. MRI scanning only to be performed as EoT/withdrawal procedure if not performed within the last 8 weeks.
o. 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.
p. CSF sampling only to be performed as withdrawal procedure in case of withdrawal prior to Visit 18/Week 48 and for patients with EoTDBP at Visit 18/Week 48. Patients with EoTDBP after Visit 18/Week 48 will not undergo CSF sampling as part of the EoTDBP procedures.
q. 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 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.
r. 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.
s. Including recording of use of feeding tube and/or wheelchair.
t. Different versions will be used: “Baseline/Screening” version at Visit 1 and at Visit 3 and “Since last visit” version at subsequent visits.
u. Exploratory gene expression profiling (RNA) and metabolomics/proteomics are an integrated part of the study and are covered by the main *Informed Consent Form.*
v. Sampling for pharmacogenetics is optional and a separate signed *Informed Consent Form* must be in place to cover this analysis.

w. Only for women of childbearing potential. If positive, confirm with serum pregnancy test.
x. Exit interview subset: at the US sites, the patients and caregivers will undergo the Exit interviews via telephone or web conferencing platform (for example, Microsoft Teams). The Exit interview will be conducted within 3 weeks after the EoTDBP Visit or within 3 weeks after the Withdrawal Visit for patients who reach a 48-week treatment period but withdraw prior to the EoTDBP 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 (for example, Microsoft Teams). The Study Experience interview will be conducted within 6 weeks after the completed Exit interview for patients who consent.

Panel 3 Optional Open-label Extension Period

Visit Name	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	EoTOLE	Withdrawal[a]	SFU-E[b]
Visit Number	Baseline **1E**	**2E**	**3E**	**4E**	**5E**	**6E**	**7E**	**8E**	**9E**	**10E**	**11E**	**12E**		**WD**	
Week[c]	**0E**	**4E**	**8E**	**12E**	**16E**	**20E**	**24E**	**28E**	**32E**	**36E**	**40E**	**44E**			
Visit Number	**13E[d]**	**14E**	**15E**	**16E**	**17E**	**18E**	**19E**	**20E**	**21E**	**22E**	**23E**	**24E**	**25E**		**26E**
Week[c]	**48E**	**52E**	**56E**	**60E**	**64E**	**68E**	**72E**	**76E**	**80E**	**84E**	**88E**	**92E**	**96E**		**112E**
Visit Window[e] (days relative to nominal visit)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**
Signed informed consent	√														
Efficacy Assessments															
UMSARS	√[f]			√			√			√			√	√	
CGI-S	√[f]			√			√			√			√	√	
PGI-S	√[f]			√			√			√			√	√	
SE-ADL	√[f]						√						√	√	
EQ-5D-5L	√[f]						√						√	√	
MRI scans: vMRI[g]	√[f,h]												√	√	
Blood sampling for NfL	√						√						√	√	
Pharmacokinetic Assessments															
Blood sampling for IMP quantification	√[f]						√						√	√	√
Pharmacodynamic Assessments															
Blood sampling for α-synuclein	√[f]						√						√	√	√
Safety Assessments															
AEs	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Blood and urine sampling for clinical safety laboratory tests	√[f]						√						√	√	
Blood sampling for ADA	√[f]						√						√	√	√
Vital signs[i]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Examinations[j] (physical, neurological)	√[f]						√						√	√	
C-SSRS since last visit	√[f]	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Visit Name	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP	EoTOLE	Withdrawal[a]	SFU-E[b]
Visit Number	Baseline **1E**	**2E**	**3E**	**4E**	**5E**	**6E**	**7E**	**8E**	**9E**	**10E**	**11E**	**12E**		**WD**	
Week[c]	**0E**	**4E**	**8E**	**12E**	**16E**	**20E**	**24E**	**28E**	**32E**	**36E**	**40E**	**44E**			
Visit Number	**13E[d]**	**14E**	**15E**	**16E**	**17E**	**18E**	**19E**	**20E**	**21E**	**22E**	**23E**	**24E**	**25E**		**26E**
Week[c]	**48E**	**52E**	**56E**	**60E**	**64E**	**68E**	**72E**	**76E**	**80E**	**84E**	**88E**	**92E**	**96E**		**112E**
Visit Window[e] (days relative to nominal visit)		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**±7**
Biobanking																
Blood sampling for ADA	√[f]						√						√	√	√
Other Study Procedures and Assessments																
IMP administration[i]	√	√	√	√	√	√	√	√	√	√	√	√			
Concomitant medication	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Urine pregnancy test[k]	√[f]	√	√	√	√	√	√	√	√	√	√	√	√	√	

ADA = anti-drug antibody; AE = adverse event; CGI-S = Clinical Global Impression – Severity of Illness; C-SSRS = Columbia-Suicide Severity Rating Scale; EoTDBP = End-of-Treatment Double-blind Period; EoTOLE = End-of-treatment of OLE; EQ-5D-5L = EuroQol 5-Dimensions, 5-Levels; IMP = investigational medicinal product; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; NfL = neurofilament light chain; OLE = Open-label Extension Period; PGI-S = Patient Global Impression-Severity of Illness; SAE = serious adverse event; SE-ADL = Schwab & England Activities of Daily Living; SFU-E = Safety Follow-up Extension; 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 SFU-E Visit will take place 16 weeks after Visit 25E/20 weeks after last IMP administration in case of withdrawal (follow-up of adverse events on-going at EoTOLE or withdrawal, and new adverse events and SAEs).
c. All assessments may be completed over a maximum of 2 days (except for MRI, see footnote g); 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. Visit 13E should occur at Week 48E, 4 weeks after Visit 12E. However, in the exceptional cases where sites have not yet received IRB/EC approval for Protocol Edition 6.0, Visit 13E can be delayed until approval is in place but no later than 5 months after Visit 12E.
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 Visit 1E.
f. Only applicable for patients who enter the OLE more than 1 week after the EoTDBP Visit.
g. 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.
h. MRI scanning only to be performed at Visit 1E if not performed within the last 8 weeks.
i. Blood pressure and pulse will be measured immediately prior to IMP administration and patients will be monitored immediately after IMP administration inclusive of saline flush (±5 minutes) for immediate drug reactions for a minimum of 2 hours with vital signs taken every 30 minutes (±5 minutes) from the end of the saline flush or until stable, whichever is later (applicable only through Visit 12E). Beginning at Visit 13E,

blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes).

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

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

2 Introduction

2.1 Background

2.1.1 Overview

Multiple system atrophy (MSA) is a sporadic, rapidly progressing neurodegenerative disorder characterized by autonomic failure, parkinsonism and/or cerebellar symptoms (multiple system atrophy parkinsonian type [MSA-P] and multiple system atrophy cerebellar type [MSA-C], respectively). Most patients are diagnosed with MSA between 50 to 60 years of age and the mean survival from onset of symptoms is 6 to 10 years, with few surviving more than 15 years.[1,2]

The pathogenesis of MSA is linked to the misfolding of α-synuclein monomers and its pathological hallmark is the presence of inclusions of misfolded α-synuclein (glial cytoplasmic inclusions [GCIs]) in oligodendroglia cells. The glial cells survive, while there is a loss of neurons in several brain areas, particularly in the *putamen*, *substantia nigra*, *pons*, *inferior olive*, and *cerebellum*. Neuronal inclusions also occur in MSA, most frequently in the *putamen*, *pontine nuclei*, and *inferior olivary nucleus*. Oligodendrocytes express little α-synuclein messenger ribonucleic acid (mRNA), either normally or in MSA, supporting the neuronal origin of α-synuclein seeds spreading the pathology. Animal models support cellular release and uptake as the mechanism of progression and spreading of the pathology.

MSA is an orphan disease. The prevalence ranges from 2 to 5 per 100,000 in the United States (US) and European Union (EU)[3] and from 7 to 20 per 100,000 in Japan.[4] MSA-P constitutes approximately 70% of the cases in the US and EU, while this ratio is inverted in Japan with MSA-C constituting approximately 70% of the cases in Japan.

There is a sigmoid progression of clinical impairment and deficits over time. A preclinical stage without apparent functional impairment or clinical features might be a phase when pathological changes are starting to accumulate without apparent deficits. This phase is followed by a stage of evolving early disease, which is clinically non-specific and escapes current consensus criteria. A phase with steep progression follows; captured by current consensus criteria, this phase represents patients diagnosed at an early stage who fulfil the possible or probable MSA criteria by having a low Unified Multiple System Atrophy Rating Scale (UMSARS) score. Finally, patients reach a late plateau phase that almost invariably meets the consensus criteria for probable MSA.[5]

No disease-modifying therapies are currently available. The management of the disease involves purely symptomatic treatments, that is, medications to stabilize and raise blood pressure and medications, such as levodopa, to reduce Parkinson's disease-like signs and symptoms. However, only a subset of MSA patients benefit from levodopa. Dopamine-agonists are not considered a therapeutic option due to poor efficacy and risk of worsening orthostatic hypotension.[6] There are no therapies that can slow down disease progression by inhibiting the neurodegenerative processes leading to neuronal cell loss. Thus,

due to the fatality and lack of effective treatments, there is an unmet need for a treatment that can delay the progression in MSA.

2.1.2 Nonclinical Data

Lu AF82422 is an anti-α-synuclein human immunoglobulin G1 monoclonal antibody (mAb), which was identified from screening hybridomas derived from transgenic mice that express human antibodies (BMS/Medarex HumAb mice). A panel of *in vitro* and *in vivo* studies were performed to select Lu AF82422 that met the following desired criteria (more details are provided in the Investigators Brochure [IB][7]):

- Binds to recombinant α-synuclein and α-synuclein isolated from disease brain tissue
- Does not cross-react with the nearest homologous, beta- and gamma-synuclein
- Recognizes all major species of α-synuclein oligomers and fibrillar forms and N- or C-terminal truncated forms of the protein
- Inhibits C-terminal proteolytic cleavage of α-synuclein
- Binds to rodent, cynomolgus, and human α-synuclein
- Inhibits seeding and aggregation of α-synuclein in cellular and animal models

Safety pharmacology assessments revealed no Lu AF82422-related adverse effects on central nervous system (CNS) (rats and monkeys), cardiovascular (monkeys), or respiratory function (monkeys).

The 4-week repeat-dose toxicity studies in rats and cynomolgus monkeys showed that Lu AF82422 was well tolerated when administered intravenously (IV) every 10 days, with no treatment-related observations or adverse findings and no observed adverse effect level (NOAEL) at the highest dose tested; 600 mg/kg/10 days.

The nonclinical immunotoxicity assessment, with focus on blood cells and neurons, did not suggest Lu AF82422-related risks of immunotoxicity.

2.1.3 Clinical Data

A first-in-human (FIH) study (Study 17699A) with Lu AF82422 in healthy subjects and patients with progressive disease (PD) has been conducted. As of Nov 2021, the *Clinical Study Report* is not yet final, and the results are considered preliminary. Fifty-eight healthy subjects and 15 patients with Parkinson's disease were exposed to Lu AF82422 or placebo (Part A, Cohorts A1-A6 in healthy subjects + Part B, Cohort B1-B2 in patients with PD) with a single dose of 75 mg (Cohort A1) to 9000 mg (Cohort A6) and 2250 mg (Cohort B1) and 9000 mg (Cohort B2). Cohort A4 to A6 included 50% Japanese healthy subjects, giving a total of 17 Japanese subjects dosed.

Target engagement (TE) of Lu AF82422 binding to α-synuclein was measured by the percentage of free α-synuclein in plasma (not bound to Lu AF82422). The data from Part A showed a good correlation between plasma concentrations of % free α-synuclein and Lu AF82422 plasma concentrations. The IC_{50} was close to that observed from *in vitro*

binding. Data demonstrated TE in plasma and pharmacokinetic (PK) properties as expected for a human IgG1, with an apparent elimination half-life ($t_{½}$) of approximately 30 days.

The treatment-emergent adverse events (TEAEs) were all non-serious, mainly mild, and did not reveal any safety concerns; Lu AF82422 was safe and well tolerated.

No safety concerns have been raised regarding infusion-related reactions, immunotoxicity, or platelet function based on the data from the FIH single ascending dose (SAD) study 17699A.

The outcome of the FIH SAD study was used to support a potential approach for Lu AF82422 to treat other α-synucleinopathies, and specifically MSA.

2.2 Rationale for the Study

MSA is a progressive, fatal disorder characterized by autonomic failure and parkinsonism and/or cerebellar involvement. Neuropathologically, MSA is characterized by oligo-dendroglial inclusions of abnormally aggregated α-synuclein. No disease-modifying therapies are currently available; symptomatic treatment options are limited, and the therapeutic benefit of these therapies is often only transient. Thus, there is a critical unmet need for a treatment that can delay the progression in MSA. α-synuclein is considered a valid target for immunotherapies that aim to neutralize and/or clear toxic α-synuclein species, Lu AF82422 is a human IgG1 mAb that recognizes all major species of α-synuclein and is being developed as a treatment for delaying of disease progression in idiopathic PD and/or MSA.

Nonclinical and clinical data of Lu AF82422 supports its potential as a safe and well tolerated treatment to reduce or inhibit seeding of pathological form(s) of α-synuclein, and potentially delay disease progression in MSA.

A FIH SAD study was conducted in healthy non-Japanese and Japanese subjects and in patients with Parkinson's disease. The main objectives of the FIH SAD study were to evaluate the safety and tolerability of Lu AF82422, to investigate the PK properties of Lu AF82422, to investigate the cerebrospinal fluid (CSF)/plasma ratio of Lu AF82422, and to evaluate the immunogenicity of Lu AF82422 following single ascending doses. 73 subjects/patients were administered a single IV infusion of Lu AF82422. The dose range was 75 to 9000 mg. Data demonstrated TE in plasma and PK properties as expected for a human IgG1, with a $t_{½}$ of approximately 30 days and no treatment-related serious adverse events (SAEs). The outcome of the FIH SAD study was used to support a potential approach for Lu AF82422 to treat other α-synucleinopathies, and specifically MSA.

2.3 Benefit – Risk Assessment

2.3.1 Overall Benefit – Risk Conclusion

Benefit

There are no therapies that can slow down disease progression by inhibiting the neurodegenerative processes leading to neuronal cell loss. Thus, due to the fatality and lack of effective treatments, there is a high unmet need for a treatment that can delay the disease progression in MSA. α-synuclein is considered a valid target for therapies that aim to neutralize and/or clear toxic α-synuclein species, thus potentially providing a beneficial outcome on the disease course.

Risks and Risk Mitigations

In general, toxicity results obtained from nonclinical studies with Lu AF82422 do not reveal any potential risk for humans and have not identified specific safety issues. In an FIH SAD study, safety data with Lu AF82422 had not raised any clinical safety concerns at doses up to 9000 mg, supporting that Lu AF82422 is considered safe and well tolerated.

The target, α-synuclein, is primarily expressed in blood cells and neurons in the CNS and the peripheral nervous system. Therefore, the following will be closely monitored: immunogenicity and major CNS-related effects. As for all mAbs, there is a potential risk of infusion-related reactions, including systemic hypersensitivity reactions, which is why Lu AF82422 is administered in a clinical facility at the study site under medical supervision with appropriate measures for adequate treatment in place. Per protocol, patients are required to be closely monitored during the infusion and with regular vital sign measurements for at least 2 hours from end of infusion (EOI). Patients will be requested to stay longer should the investigator determine this is clinically warranted.

In addition to the above, the following risk mitigations are also taken for hypersensitivity reactions;

- History of severe drug allergy, anaphylaxis or hypersensitivity or known hypersensitivity or intolerance to the investigational medicinal product (IMP) or its excipients is an exclusion criterion.
- Severe and/or serious systemic hypersensitivity reaction to IMP infusion or any anaphylactic reaction, confirmed by a clinically relevant increase of serum total tryptase from baseline level is a withdrawal criterion.

To monitor patient safety, blinded safety data will be reviewed regularly by internal medical monitoring and safety review and by the Lundbeck Lu AF82422 Safety Committee to ensure that prompt action can be taken. In addition, an independent Data Monitoring Committee (iDMC) will regularly review/analyze the unblinded patients' safety data according to the iDMC Charter in the double-blind period (DBP).

The risks associated with this study are considered adequately elucidated in the nonclinical studies and in the FIH SAD study, well controlled by cautionary measures in the study design,

and well balanced with the potential benefits of the treatment; a potentially effective treatment to delay disease progression in MSA.

Lundbeck considers the benefit/risk profile of this study (18331A) to be acceptable based on the available nonclinical and clinical data for Lu AF82422.

2.3.2 COVID-19 Related Risk Assessment and Mitigation

Appropriate risk assessment has been performed and mitigations to be done in case of restrictions due to coronavirus disease 2019 (COVID-19) are described in detail in a separate "COVID-19 Mitigation Plan".

3 Objectives and Endpoints

The study objectives and endpoints are summarized in Panel 4.

Panel 4 Objectives and Endpoints

Objectives and Endpoints	
Objectives	**Endpoints**

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)
	Disease progression
	• Primary endpoint:
	  • 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 End-of-Treatment of the DBP (EoTDBP)
	• Key secondary endpoint:
	  • Disease progression, as assessed by longitudinal changes from baseline in modified UMSARS Part I (mUMSARS) score up to EoTDBP
	• Secondary endpoints:
	  • Disease progression, as assessed by longitudinal changes from baseline in the UMSARS Part I and UMSARS Part II scores up to EoTDBP
	  • Change from baseline up to Week 48 in the DBP in UMSARS TS, UMSARS Part I, mUMSARS and UMSARS Part II scores
	• Exploratory endpoint:
	  • Disease progression, as assessed by longitudinal changes from baseline in the abbreviated UMSARS (aUMSARS) up to EoTDBP

Secondary Objectives
• To evaluate the efficacy of Lu AF82422 on:
  • Function
  • Global impression, severity of illness during the DBP
	Function
	• Secondary endpoint:
	  • Change from baseline to Week 48 in the DBP in Schwab and England Activities of Daily Living (SE-ADL) score
	
	Global impression
	• Secondary endpoints:
	  • Change from baseline to Week 48 in the DBP in Clinical Global Impression – Severity of Illness (CGI-S) score
	  • Change from baseline to Week 48 in the DBP in Patient Global Impression – Severity of Illness (PGI-S) score
	  • Change from baseline to Week 48 in the DBP in Observer-reported Global Impression – Severity of Illness (OGI-S) score

Objectives and Endpoints	
Objectives	**Endpoints**

Secondary Objectives (continued)
 	
• To evaluate the efficacy of Lu AF82422 on:
  • Autonomic symptoms
  • Global disability
  • Disease milestones
  • Health-related quality of life during the DBP
	Endpoints (continued)
	
	Autonomic symptoms
	• Secondary endpoint:
	• Change from baseline to Week 48 in the DBP in Composite Autonomic Symptom Scale Select Change (COMPASS Select Change) score
	• Exploratory endpoint:
	• Change from baseline to Week 48 in the DBP in heart rate, blood pressure, and orthostatic symptoms, as assessed in UMSARS Part III
	
	Global disability
	• Secondary endpoint:
	• Change from baseline to Week 48 in the DBP in UMSARS Part IV score
	
	Disease milestones
	• Secondary endpoints:
	• Change from baseline to Week 48 in the DBP in speech, swallowing, falls and walking, as assessed by the UMSARS Part I item scores
	• Change from baseline to Week 48 in the DBP in frequency, cause and consequence of falls, as assessed by the fall diary periods
	• Exploratory endpoints:
	• Time to wheelchair use
	• Change from baseline to Week 48 in the DBP in frequency of falls, as assessed by PAMSys (subset)
	• Change from baseline to Week 48 in the DBP in gait parameters, as assessed by FeetMe® (subset)
	
	Health-related quality of life
	• Secondary endpoint:
	• Change from baseline to Week 48 in the DBP in EuroQol 5-dimension, 5-level (EQ-5D-5L) score

• To evaluate the efficacy of Lu AF82422 on disease progression, as measured by brain magnetic resonance imaging (MRI)	**MRI biomarkers**
	• Secondary endpoint:
	  • Percentage change from baseline to Week 48 in the DBP 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)
	• Exploratory endpoints:
	  • Percentage change from baseline to Week 48 in the DBP 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
	  • Percent change from baseline to Week 48 in the DBP in cerebral blood flow (CBF) in ROIs; putamen and cerebellum, as measured by arterial spin labelling (ASL) MRI

Objectives and Endpoints	
Objectives	**Endpoints**

Secondary Objectives (continued)
• To evaluate the efficacy of Lu AF82422 on biofluid biomarkers of disease progression during the DBP
	Endpoints (continued)
	
	Biofluid biomarkers
	• Secondary endpoint:
	  • Blood biomarkers: Change from baseline up to Week 48 in the DBP in neurofilament light chain (NfL) concentrations
	• Exploratory endpoints:
	  • Cerebrospinal fluid (CSF) biomarkers: Change from baseline up to Week 48 in the DBP in t-tau and NfL concentrations

• To evaluate the pharmacokinetics of Lu AF82422	**Pharmacokinetics**
	• Secondary endpoints:
	  • Lu AF82422 plasma concentration during treatment and Safety Follow-up
	  • Lu AF82422 CSF concentrations and the CSF/plasma concentration ratios at Week 48 in the DBP

Objectives and Endpoints	
Objectives	**Endpoints**
Exploratory Objectives	**Endpoints (Exploratory)**

• To explore the target engagement (TE) of Lu AF82422 to α-synuclein during the DBP	• Blood:
	  • Plasma concentrations of "free" and "total" α-synuclein during treatment and Safety Follow-up
	• CSF:
	  • Concentrations of "free" and "total" α-synuclein at baseline and Week 48 in the DBP

• To explore the TE of Lu AF82422 to pathological species of α-synuclein during the DBP	• CSF biomarkers: • Changes from baseline up to Week 48 in the DBP in pathological species of α-synuclein

• To explore the relationship between UMSARS, MRI parameters and NfL during the DBP	• Relationship between:
	  • Change from baseline to Week 48 in the DBP in UMSARS TS, Part I and Part II scores,
	  • Percentage change from baseline to Week 48 in the DBP in brain volume and tissue integrity in brain ROIs as measured by MRI, and
	  • Change from baseline up to Week 48 in the DBP in NfL concentrations.

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

Objectives and Endpoints	
Objectives	**Endpoints**

Exploratory Objectives
 	
• To explore the efficacy of Lu AF82422 for up to 72 weeks of treatment on clinical scales and biomarkers during the DBP
	Endpoints (Exploratory)
	
	• Clinical scales:
	  • Change from baseline to EoTDBP in UMSARS Part I items 1, 2, 7 and 8, Part III and Part IV, and SE-ADL, CGI-S, PGI-S, OGI-S, COMPASS Select Change and EQ-5D-5L
	• Blood biomarkers:
	  • Change from baseline to EoTDBP in NfL concentrations
	• MRI biomarkers:
	  • Change from baseline to EoTDBP in vMRI, DTI and ASL measures

• To collect patient experience with impaired functions due to MSA to support the interpretation of change during the study (*Exit Interview subset*) during the DBP	• Describe patient experience data and meaningful change (for example, symptoms, function, quality of life and disease manifestations) from the patient's and caregiver's perspective, as assessed by the Exit interviews
• To collect patient experience with study participation (Study Experience Interview subset) during the DBP	• Describe patient experience data (for example, study experience, operational considerations, satisfaction with study experience, suggestions) from the patient's and caregiver's perspective, as assessed by the Study Experience interviews
Safety Objective To evaluate the safety and tolerability of Lu AF82422 in patients with MSA in the DBP To evaluate safety and tolerability of Lu AF82422 in patients with MSA in the OLE	**Safety Endpoints** Double-blind Period • Treatment-emergent adverse events • Absolute values and changes from baseline in clinical safety laboratory test values, vital signs, weight, and electrocardiogram (ECG) parameter values • Development of specific anti-drug antibodies (ADAs) • Findings on MRI, as specified in the Imaging Charter • Columbia-Suicide Severity Rating Scale (C-SSRS) score 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 ADAs • C-SSRS score

4 Study Design

4.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[8]

This is a phase II, interventional, randomized, double-blind, parallel-group, placebo-controlled, including an optional open-label extension (OLE), 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 Unified Multiple System Atrophy Rating Scale Total Score (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 study design is presented in Panel 1 and the scheduled study procedures and assessments for the DBP are summarized in Panel 2 and for OLE assessments are summarized in Panel 3.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[9] and applicable regulatory requirements.

60 patients, recruited from specialist centres, are planned for randomization: 40 patients in the Lu AF82422 CCI group and 20 patients in the placebo group.

The target population for this study are patients with possible or probable MSA, as defined by the current consensus diagnostic criteria (see Appendix V). 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.

In the DBP, patients will be randomized to Lu AF82422 CCI or placebo (2:1) via a centralized randomization system (Interactive Response Technology [IRT]). To ensure a balanced treatment allocation, stratification will be applied according to two factors, that is, CCI and Region (US/Japan, with a maximum of 25% of patients from Japan). Patients with a missing CCI will be stratified to a separate group labelled “missing”.

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 166 to 190 weeks for patients continuing in the OLE. The study includes the following periods:

- Screening Period (4 weeks)
- Randomization Period (2 weeks)
- DBP (48 weeks up to 72 weeks)
- Optional OLE (96 weeks)
- Safety Follow-up Period (20 weeks after last IMP administration)

All patients entering the OLE will receive Lu AF82422 CCI during the OLE. Patients who enter the OLE will receive the first open-label dose (Visit 1E) on the same day as the End-of-Treatment Visit for the DBP (EoTDBP) or as soon as possible thereafter, but no later

than 5 months after the EoTDBP Visit, and will be enrolled into OLE no later than the end of Q1 2024. If a Safety Follow-up Visit for the DBP is due before the OLE is implemented, it should be completed per Panel 2. The patient could afterwards enter the OLE and treatment could continue for a planned period of 96 weeks. OLE procedures will be performed as presented in Panel 3.

In the OLE, patients will receive Lu AF82422 until Visit 24E (Week 92E) and complete the EoTOLE at Visit 25E (Week 96E). Visit 13E should occur at Week 48, 4 weeks after Visit 12E. However, in the exceptional cases where sites have not yet received Institutional Review Board (IRB)/Ethics Committee (EC) approval for Protocol Edition 6.0, Visit 13E can be delayed until approval is in place but no later than 5 months after Visit 12E.

Patients who do not consent to the optional OLE will enter the Safety Follow-up Period after the EoTDBP.

The individual DBP 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. The remaining patients in the DBP will have their next scheduled visit converted to an EoTDBP Visit with assessments as listed for Visit 24, as according to Panel 2.

During the DBP, patients will attend IMP Visits to follow a dosing schedule with either Lu AF82422 or placebo every 4 weeks (Q4W).

Patients who withdraw, except for those who withdraw their consent, will be scheduled for a Withdrawal Visit to undergo clinical and safety assessments as soon as possible.

All patients (except the ones withdrawing consent) will be scheduled for a Safety Follow-up Visit 20 weeks after their last IMP dose, regardless if they received their last dose in the DBP or OLE, or if they withdrew.

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 from the end of the saline flush or until stable, whichever is later (applicable only through Visit 12E).

Beginning at Visit 13E, blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes).

CSF assessments for evaluation of PK, TE, and biomarkers at baseline and after initiation of treatment will be collected according to Panel 2. CSF sampling is 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.

At all the US sites, additional assessments (objective sensor-based assessments and qualitative interviews) will be performed (hereafter referred to as the “Sensor subset” and “Exit Interview

subset"). Participation in the Exit Interview subset is mandatory for patients and caregivers, while participation in the Sensor subset is optional. Patients who wish to participate in the Sensor subset must provide specific consent to one or both devices as part of the main *Informed Consent Form*. Patients can withdraw from these additional assessments without having to withdraw from the main study. Additionally, at US sites, a subset of patients and caregivers may be contacted about an opportunity to participate in an additional interview about study experience ("Study Experience Interview subset").

- Patients from the Sensor subset will be subject to additional objective sensor-based assessments using the PAMSys and/or FeetMe® devices. These devices will collect data on the patient's gait and events of fall (sections 10.2.1.9 and 10.2.1.10). The devices will passively collect data in the remote environment starting from the Randomization Visit until the Baseline Visit, and then for four pre-defined periods during the DBP according to Panel 2. The devices will be handed out to patients and returned by patients at standard in-clinic visits.
- Patients and caregivers from the Exit Interview subset will participate in an Exit interview via web conferencing platform (for example, Microsoft Teams) or telephone. The Exit interviews will take place approximately 3 weeks after the EoTDBP Visit or Withdrawal Visit. For patients withdrawing from the study, the Exit interview will only be performed if they have been in the DBP for at least 48 weeks. The content of the Exit interviews may reveal potential adverse events (PAEs) that occurred between EoTDBP/Withdrawal Visit and the conduct of the interview (section 10.7.1).
- A subset of patients and caregivers at US sites may be contacted to participate in a Study Experience interview. The interview will focus on the overall Study Experience from the perspective of the patient and caregiver, including topics such as logistical considerations, satisfaction with participation in the study, and suggestions for improvement for future studies. The interviews will follow a separate interview protocol and will be conducted by ICON. The content of the Study Experience interviews may reveal PAEs that occurred between and the conduct of the Exit interview and the Study Experience interview (section 10.7.2).

An iDMC will regularly monitor the patients' unblinded safety data according to the DMC Charter during the DBP (more information is provided in section 11.6).

4.2 Rationale for the Study Design

In preparation for this study, Lundbeck conducted a qualitative patient insight research to understand MSA patients' needs and collect feedback on a preliminary visit schedule. A total of 10 MSA patients and 5 caregivers in the US, United Kingdom, and Germany were interviewed to gain patient insights. These patient insights and concerns were considered when planning procedures and the design of the current study. In these interviews, patients understood the need for a tight study schedule and were interested in a close monitoring of their disease. Overall, these efforts are in consideration of MSA patients' needs and challenges, ultimately supporting patient centric study design and protocol.

This protocol is targeting an early population of MSA patients, allowing patients with either MSA-P or MSA-C and including only patients with an UMSARS Part I score ≤16 (omitting

item 11). In addition, selected features of MSA, such as falling and gait disturbances, will be investigated in a subgroup of patients outside the clinic in their home environment by applying wearable sensors for 2 weeks during the Randomization Period and 10 consecutive days (FeetMe®) and 4 weeks (PAMSys), four times during the treatment period.

This is a phase II, interventional, randomized, double-blind, parallel-group, placebo-controlled, including an optional OLE, multi-centre study of the efficacy (slowing disease progression), safety, and tolerability of Lu AF82422 in patients with MSA. The treatment duration of 48 to 72 weeks for patients not entering the optional OLE period and between 166 to 190 weeks for patients continuing in the OLE is considered a reasonable time window to investigate the natural progression of disease. Collection of safety and tolerability data for this period will be of substantial value for an immunotherapy intended for chronic use.

Based on data from the PK results from FIH SAD study, a clearance of approximately 0.25 L/day, a plasma t½ of approximately 28 to 30 days and a CSF/plasma concentration ratio of approximately CCI, the predicted CSF steady state concentrations may give rise to up to CCI TE to α-synuclein oligomeric forms at the selected fixed dose (body weight 70 kg): CCI CCI Q4W.

Inclusion of a placebo group is justified since, to date, no drug has an indication for delaying disease progression in patients with MSA. The randomization ratio increases the possibility that the patient will receive an active treatment during the DBP.

Since there are currently no available treatments for MSA, Lundbeck wishes to offer patients to continue with, or for patients initially receiving placebo, to receive Lu AF82422 for up to 96 weeks in the optional OLE. The data collected during the OLE will provide additional information on long-term safety and effect and on the effect of a delayed-start with Lu AF82422 for patients originally randomized to placebo as compared to patients being on Lu AF82422 throughout the DBP and the OLE. This additional information will contribute to the understanding of the compound in relation to effect size, when a possible effect will be detectable, and if slightly more advanced patients will benefit to the same extent as less advanced patients.

Patients participating in this study can be on stable treatment for managing their MSA symptoms, and if needed during the study, change or initiation of treatment for managing MSA symptoms is allowed per investigator discretion. Thus, no patient will be denied access to standard treatments.

The sample size for the primary endpoint is based on CCI CCI CCI Magnetic resonance imaging (MRI) biomarkers are included as secondary endpoints to investigate if the delay in clinical progression is supported by a delay in the underlying neuropathological process. The inclusion of blood and CSF biomarkers as secondary endpoints will allow the understanding of any downstream biomarker effects of potential α-synuclein reduction and the establishment

of a clear link between biomarker and clinical endpoints. Exit interviews will facilitate interpretation of meaningful change from a patient and caregiver perspective.

The study is designed in accordance with regulatory guidance.

5 Ethics

In general, toxicity results obtained from nonclinical studies with Lu AF82422 do not reveal any potential risk for humans and have not identified specific issues. Safety data with Lu AF82422 have not raised any clinical safety concerns following a single dose up to 9000 mg in healthy volunteers and patients with Parkinson's disease from the completed FIH SAD study, supporting that Lu AF82422 can be safely used in the proposed clinical phase II study in patients with MSA.

The target, α-synuclein, is primarily expressed in blood cells and neurons in the CNS and the peripheral nervous system, therefore the following will be closely monitored: immunogenicity and major CNS-related effects. As for all mAbs, there is a potential risk of infusion-related reactions, including acute systemic hypersensitivity reactions, which is why close monitoring of patients with regular vital sign measurements for 2 hours post-dose will take place.

The risks associated with this study are considered adequately elucidated in the nonclinical studies and in the FIH SAD study, well controlled by cautionary measures in the study design, and well balanced with the potential benefits of the treatment; a potentially effective treatment to delay disease progression in MSA.

5.1 Ethical Rationale

The ethical rationales for this study are the following:

- There is an unmet medical need for a treatment that can delay the progression in MSA, addressed by this study
- The justification of the study design is provided in section 4.2
- Establishing an iDMC because:
  - MSA is a new indication, and in the FIH SAD study only a few patients with another type of α-synucleinopathy (Parkinson's disease) were exposed to Lu AF82422. No MSA patients have previously been exposed to Lu AF82422.
  - Use of a mAb, a new therapeutic, where other entities of the class had effects on the CNS.
  - Limited safety data overall are available on Lu AF82422 (low number of subjects exposed to a single dose of Lu AF82422).

The patient will be fully informed about the study including the risks and benefit of his/her participation in the study.

The patient may withdraw from the study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled.

Information on race will be collected to support future filing claims in the US according to Food and Drug Administration (FDA) guidance document[12] and ICH E17 guideline on general principles for planning and design of multi-regional clinical trials.[13]

In accordance with *Good Clinical Practice*,[9] qualified medical personnel at Lundbeck or designated clinical research organization (CRO) will be readily available to advise on study-related medical questions. Medical monitoring and safety review will be performed throughout the study. In addition, safety data will be reviewed regularly by the Lundbeck Lu AF82422 Safety Committee to ensure that prompt action is taken, if needed.

In accordance with *Good Clinical Practice*,[9] the investigator will be responsible for all study-related medical decisions.

5.2 Informed Consent

No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the patient and the caregiver. An informed consent is required for patients in the optional OLE.

Informed Consent for the Patient: The patient *Informed Consent Form* will explain the purpose, benefits and risks of the study, the details of their involvements, services and compensations. In the US, the main informed consent will in addition include participation in the Exit Interview subset for patients, optional participation in the PAMSys and FeetMe® assessments as well as the optional exploratory laboratory assessments detailed below.

Informed Consent for the Caregiver: The caregiver *Informed Consent Form* will explain the purpose, benefits and risks of the study, the details of their involvements, services and compensations. It will also describe the treatment of confidential information. In the US, the caregiver informed consent will also include participation in the Exit Interview subset for patient and caregivers. In case the caregiver drops out before the study ends, a new caregiver should be identified. The new caregiver should participate in the Exit interview. However, the patient can remain in study if no new caregiver can be identified.

In case of pregnancy, please refer to section 11.2.

It is the responsibility of the investigator or person designated by the investigator to obtain written informed consent from the patient and the caregiver(s). If the informed consent process may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

The investigator must identify vulnerable patients, that is, patients whose willingness to participate in this study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior

members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

Prior to obtaining written informed consent, the investigator or a designee must explain to the patients and the caregiver(s) the aims and methods of the study and any reasonably expected benefits and foreseeable risks or inconveniences to the patients.

The patients must be informed:

- that their participation in the study is voluntary and that they are free to withdraw from the study at any time without justifying their decision
- of the possibility of withdrawing consent (section 6.4)
- of their right to request a copy of their personal data from the study via the investigator
- of their right to be informed by the investigator, after the study has been reported, about which treatment they received
- of their right to receive information about the study results from the investigator on the patient's own initiative; the results will be available approximately 1 year after the end of the study

The patients must be informed that persons authorized by Lundbeck and authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ECs or IRBs) may view their medical records. The patients must also be informed that de-personalized copies of parts of their medical records may be requested by authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ECs or IRBs) for verification of study procedures and/or data. The confidentiality of the patients will, in all cases, be respected.

The patients must be given ample time and opportunity to inquire about the details of the study prior to deciding whether to participate in the study.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients prior to allowing a patient to participate in the study, an *Informed Consent Form* must be signed and dated (by the patient and signed and dated by the investigator or a designee on the same day). The patient must be given a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Consent Form*.

The consent procedures described above will only be implemented if allowed by local law and regulations and will only be initiated after approval by the relevant ECs.

As the blood sampling for the exploratory analyses (gene expression profiling [ribonucleic acid that is RNA] and metabolomics/proteomics) is an integral part of this study, the main *Informed Consent Form* covers these analyses. Conversely, the blood sampling for potential future genetic biomarker analysis is optional and a separate *Informed Consent Form* covers this analysis.

The blood and CSF samples for potential future exploratory biomarker analysis, or the data derived from these blood samples, may be shared with academic and public institutions and other companies. However, Lundbeck will retain full control of the samples and their use in accordance with the information in the *Informed Consent Form*.

A patient may, at any time and without stating a reason, specifically request the destruction of the patient's deoxyribonucleic acid (DNA) sample, irrespective of the patient's continued participation in the study. The investigator must send a written request on behalf of the patient to the Lundbeck international study manager. The investigator will receive written confirmation from Lundbeck when the DNA sample has been destroyed.

5.3 Personal Data Protection

The data collected in this study will be processed in accordance with the specifications outlined in the Danish Data Protection Act and the applicable laws of the US and Japan to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck or delegate and the external organization to ensure compliance with the above-mentioned legislation.

5.4 Ethics Committee(s) and Institutional Review Board(s)

This study will be conducted only after Lundbeck has received confirmation that the regulatory authorities have approved or confirmed notification of the study and that written approval of the protocol has been granted by the appropriate EC or IRB.

The investigator must not allow any patients to participate in the study before receiving confirmation from Lundbeck or the CRO that the required approvals and/or notifications have been received.

The EC or IRB must be informed when specific types of protocol amendments have been made and written approval must be obtained before implementation of each amendment, if required by local law.

If applicable, interim reports on the study and reviews of its progress will be submitted to the EC or IRB by the investigator at intervals stipulated in its guidelines.

6 Study Population

6.1 Number of Patients and Countries

Overall, a minimum of 60 patients, recruited from specialist centres, are planned for randomization.

Planned regions include: North America (US) and Asia (Japan).

6.2 Patient Recruitment

Competitive patient recruitment between countries and sites will be used during the entire recruitment period to ensure that the required number of patients are randomized within the planned recruitment period.

The investigators will be notified immediately when the recruitment period comes to an end.

6.3 Selection Criteria

Patient selection is based on the inclusion and exclusion criteria listed below.

Patients who meet each of the inclusion criteria and none of the exclusion criteria at the Screening Visit as well as Randomization Visit are eligible to participate in this study.

Inclusion Criteria

1. The patient is capable of communicating with the site personnel
2. The patient is able to read and understand the *Informed Consent Form*
3. The patient's caregiver is able to read and understand the *Caregiver's Informed Consent Form*
4. The patient has signed the *Informed Consent Form*
5. The patient's caregiver has signed the *Caregiver's Informed Consent Form*
6. The patient is aged ≥40 and ≤75 years at the Screening Visit
7. The patient has suitable peripheral venous access for IMP administration and blood sampling
8. The patient is diagnosed with possible or probable MSA of the MSA-P or MSA-C sub-type according to the *Gilman criteria*[14] at the Screening Visit (see Appendix V)
9. The patient had onset of motor and/or autonomic (orthostatic or urinary) MSA symptoms within 5 years prior to the Screening Visit in the judgement of the investigator (applicable to patients enrolled before Protocol Version 4.0)
    a. The patient had onset of motor MSA symptoms within 5 years prior to the Screening Visit in the judgement of the investigator (applicable to patients enrolled under Protocol Version 4.0)
10. The patient has an anticipated survival of at least 3 years, in the opinion of the investigator, at the Screening Visit
11. The patient has an UMSARS Part I score ≤16 (omitting item 11 on sexual function) at the Screening Visit
12. The patient has a cognitive performance evaluated by the Montreal Cognitive Assessment (MoCA) with a score ≥22 at the Screening Visit. Add 1 point for an individual who has 12 years or fewer of formal education
13. The patient has a knowledgeable and reliable caregiver who will be available throughout the study to complete a caregiver observer questionnaires (at site visit or in a remote setting) when carer/observer-reported outcomes are performed. A caregiver is defined as

a person who spends approximately 3 hours or more with the patient per week and can inform on the patient's level of functioning

14. The patient, if a woman, must:
    - –have had her last natural menstruation ≥12 months prior to the Screening Visit, OR
    - –have been surgically sterilized prior to the Screening Visit, OR
    - –have had a hysterectomy prior to the Screening Visit, OR
    - –agree not to try to become pregnant during the study, AND accept to follow one of the following contraceptive methods:
        - o Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation for example, oral (in combination with a double barrier methods [either a condom in combination with a spermicide or a diaphragm in combination with a spermicide]), intravaginal or transdermal hormonal contraception
        - o Progesterone only hormonal contraception associated with inhibition of ovulation for example, oral (in combination with a spermicide or a diaphragm in combination with spermicide), injectable or implantable hormonal contraception
        - o Intrauterine hormone-releasing system
        - o Intrauterine devices
        - o Vasectomized partner
        - o Sexual abstinence
        - o Engaging in same-sex relationships
    - –The contraception must be used from Screening Visit and until ≥5 months after the last dose of IMP
15. The patient, if a man, must:
    - –use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit until ≥5 months after the last dose of IMP, OR
    - –have been surgically sterilized prior to the Screening Visit

Exclusion Criteria

1. The patient has previously been enrolled in this study
2. The patient has participated in a clinical study with last dose of an IMP <30 days or 5 plasma half-lives (whichever is longer) prior to the Screening Visit
3. The patient is a member of the study personnel or of their immediate families or is a subordinate (or immediate family member of a subordinate) to any of the study personnel
4. The patient is pregnant or breastfeeding
5. The patient has a history of severe drug allergy, anaphylaxis or hypersensitivity or known hypersensitivity or intolerance to the IMP or its excipients
6. The patient has any other disorder for which the treatment takes priority over treatment of MSA or is likely to interfere with the study treatment or impair treatment compliance
7. The patient has been treated with an anti-α-synuclein monoclonal antibody, mesenchymal stem cells or an inhibitor of α-synuclein aggregation within the last 12 months

8. The patient has any past or current treatment with an active vaccine targeting α-synuclein
9. The patient has two or more blood relatives with a history of MSA
10. The patient meets any of the following criteria at the Screening Visit, which suggests advanced disease (only applicable to patients enrolled before Protocol Version 4.0 and not applicable for patients enrolled under Protocol Version 4.0):
    - –Speech impairment, as assessed by a score of ≥3 on UMSARS Part I, item 1
    - –Swallowing impairment, as assessed by a score of ≥3 on UMSARS Part I, item 2
    - –Impairment in ambulation, as assessed by a score of ≥3 on UMSARS Part I, item 7
    - –Falling more frequently than once per week, as assessed by a score of ≥3 on UMSARS Part I, item 8
11. The patient has evidence (clinically or on MRI) and/or history of any clinically significant disease or condition other than MSA, for example, serious neurological disorder, other intracranial or systemic disease. Abnormalities (space-occupying lesions, vascular lesions, tumours, stroke, etc.) on MRI are to be discussed with the Lundbeck medical expert or the CRO medical monitor before the patient is enrolled
12. The patient has a current diagnosis of movement disorders that could mimic MSA; for example, Parkinson's disease, dementia with Lewy bodies, essential tremor, progressive supranuclear palsy, spinocerebellar ataxia, spastic paraparesis, corticobasal degeneration, or vascular, pharmacological or post-encephalitic parkinsonism, per investigator discretion. Patients who have previously been incorrectly diagnosed with Parkinson's disease will not be excluded
13. The patient has a history of moderate or severe head trauma or other neurological disorder or systemic medical disease that is, in the investigator's opinion, likely to affect CNS functioning
14. The patient has a history of neurosurgical procedures including deep brain stimulation that could, in the investigator's opinion, interfere with the assessments of safety or efficacy
15. The patient has contraindications for MRI
16. The patient has attempted suicide within the last 6 months or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the Columbia-Suicide Severity Rating Scale [C-SSRS] within the past 6 months)
17. The patient has a history of cancer, other than basal cell, Stage 1 squamous cell carcinoma of the skin or cured gastric or cervical carcinoma in situ, that has not been in remission for >5 years prior to the first dose of IMP
18. The patient takes or has taken recent or concomitant medication that is disallowed or allowed with restrictions (specified in Appendix II) or it is anticipated that the patient will require treatment with at least one of these medications during the study:
    - –*Disallowed*: any investigational products within 30 days before the Screening Visit, treatment targeting α-synuclein and/or MSA disease progression
    - –*Allowed with restriction*: stable dose for at least 8 weeks prior to randomization of drugs acting against parkinsonism (for example, Levodopa, Dopamine-Agonists, Amantadine and Monoamine oxidase B [MAO-B]-inhibitors) and/or drugs acting against autonomic

dysfunction (for example, ephedrine, droxidopa, midodrine, fludrocortisone, octreotide, desmopressin, oxybutynin) and anticipated stable during the DBP. If medically necessary, initiation of or change of dose of concomitant medication is allowed per investigator discretion.

19. The patient has previously tested positive for hepatitis B surface antigen (HBsAg), anti-hepatitis virus C (HCV) or human immunodeficiency virus (HIV)
20. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:
    - –a serum creatinine value >1.5 times the upper limit of the reference range
    - –a serum total bilirubin value >2 times the upper limit of the reference range. If the patient is diagnosed or suspected of having Gilbert's syndrome, the patient can be discussed with the medical monitor
    - –a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
21. The patient has, at the Screening Visit:
    - –an abnormal electrocardiogram (ECG) that is, in the investigator's opinion, clinically significant AND/OR
    - –a PR interval >225 ms OR
    - –a QRS interval ≥150 ms OR
    - –a QT_{cF} interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where $QT_{cF} = QT/RR^{0.33}$)
    - –or a QT_{cF} interval >440 ms (for men) or >460 ms (for women) if the patient has a heart rate <60 bpm (beats per minute)
22. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
23. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

Open-label Extension Entry Criteria

1. The patient has completed the EoTDBP Visit and did not withdraw in the DBP
2. The patient has consented to participate in the OLE
3. The patient has completed the EoTDBP within the last 5 months and will be enrolled into the OLE no later than end of Q1 2024
4. The patient is, in the investigator's opinion, likely to comply with the protocol
5. The patient has not received any other investigational product since the EoTDBP Visit

6.4 Withdrawal Criteria

A patient must be withdrawn from the study if:

- The patient withdraws consent (defined as a patient **explicitly** takes back his or her consent); section 9.6 states how the patient's data will be handled
- The patient has been randomized in error and has not been administered IMP
- Withdrawal of patients enrolled in error and who have received the IMP should be based on a case-by-case evaluation of the individual risk/benefit. The decision about the administration of more doses of Lu AF82422 will be based on an individual risk/benefit assessment as judged by the investigator
- The patient can no longer attend study visits due to MSA disease progression.
- The patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient])

A patient must be withdrawn from treatment if:

- The patient experiences any systemic hypersensitivity reaction to IMP infusion which are confirmed as anaphylactic reaction by a clinically relevant increase of serum total tryptase from baseline level (see section 11.1.3)
- The patient experiences any severe and/or serious systemic hypersensitivity reactions even though the serum total tryptase does not confirm an anaphylactic reaction
- The patient experiences an adverse event that, in the opinion of the investigator or sponsor's medical expert, contraindicates further dosing
- The investigator considers it, for safety, lack of efficacy, and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn from treatment
- Any site personnel breaks the randomization code for that patient
- The patient becomes pregnant
- The patient has a serum ALT or AST value >3 times the upper limit of the reference range and a serum total bilirubin value >2 times the upper limit of the reference range
- The patient has a serum ALT or AST value >5 times the upper limit of the reference range that is confirmed by testing <2 weeks later
- The patient has a QT_{cF} interval >500 ms confirmed on repeat, if the repeat is done within 72 hours; the decision to withdraw the patient may be postponed until a repeat ECG is taken, if it is taken within 72 hours during the DBP.
- A patient may be withdrawn from the study if:
  - The patient fails to comply with study procedures

Patients who withdraw will not be replaced.

7 Investigational Medicinal Product

Lu AF82422 is a human IgG1 monoclonal antibody that recognizes all major species of α-synuclein.

7.1 Treatment Regimen

7.1.1 Treatment Regimen Double-blind Period

Patients will be randomly allocated via a centralized randomization system (IRT) to one of two treatment groups:

- Lu AF82422 CCI
- placebo

Patients will be randomly allocated in ratio 2:1 Lu AF82422 CCI and placebo.

Patients will receive IMP starting from the Baseline Visit to follow a Q4W dosing schedule with either Lu AF82422 or placebo by IV infusion. Any deviation from the Q4W ±3 days dosing schedule must be discussed and agreed with the medical monitor and documented as a protocol deviation. IMP dosing must not take place if less than 2 weeks until the next scheduled IMP infusion.

All patients will receive double-blind treatment with IMP starting at baseline (Week 0) until Visit 18 (Week 48), however, some patients will continue to receive treatment up to Visit 24 (Week 72). The individual treatment period will vary from 48 weeks up to 72 weeks based on the timing of the last patient randomized. Once the last patient reaches 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 EoTDBP Visit will have their next visit converted to an EoTDBP Visit with assessments as listed for Visit 24, according to Panel 2. During the DBP, patients will attend IMP Visits to follow a dosing schedule with either Lu AF82422 or placebo Q4W. Patients who do not consent to the optional OLE will enter the Safety Follow-up Period after the EoTDBP Visit.

7.1.2 Treatment Regimen Open-label Extension Period

Patients will receive Lu AF82422 CCI.

In the OLE, all patients will receive open-label treatment with Lu AF82422 starting at Visit 1E until Visit 24E (Week 92E) (see Panel 3).

During the OLE period, any deviation from the Q4W ±3 days dosing schedule must be discussed and agreed with the medical monitor and documented as a protocol deviation. IMP dosing must not take place if less than 2 weeks until the next scheduled IMP infusion.

After Visit 25E, or if prematurely discontinued, patients will be scheduled for a Safety Follow-up Visit 20 weeks after the last IMP dose, as scheduled in Panel 3.

7.2 IMP(s), Formulation(s), and Strength(s)

The IMP(s) supplied by Lundbeck in this study are:

- Lu AF82422 solution for infusion 53 mg/mL expected dose [redacted]
- Placebo to Lu AF82422 solution for infusion

At each visit the patient will receive [redacted] of Lu AF82422 or placebo.

From each of [redacted] vials assigned in the IRT, [redacted] solution will be drawn and transferred to an empty infusion bag (to contain the total of [redacted] of IMP) and the bag will be covered. Doses will be administered by IV infusion over 30 minutes including flush of the infusion line with saline (±10 minutes).

IMP can be prepared at bed side or at the pharmacy thereafter it is transferred to the clinic for administration. In order to maintain the blind, the IMP will be prepared by unblinded, qualified study personal. Preparation has to be undertaken as soon as practicable before administration. Based on in-use stability study, shelf life on product in infusion bag is maximally 4 hours. The date and time of expiry should be stated on the dosing unit label. Details of preparation of IMP for administration are described in the *IMP Manual/Infusion guide.*

In the US, preparation can be done outside a laminar flow cabinet bench based on microbial challenge tests performed. Details of IMP administration will be described in the *IMP Manual/Infusion guide*.

In case of mild or moderate systemic hypersensitivity reaction, which is not an anaphylactic reaction, the IMP should be administered going forward in this patient with slower infusion rate (over 1 hour instead of 30 minutes). This procedure does not avoid a hypersensitivity reaction but helps reduce the severity of any potential reoccurrence. The patient must be withdrawn from treatment if in the opinion of the investigator the reaction contraindicates further dosing.

After IMP Administration

Patients will be monitored for immediate drug reactions for a minimum of 2 hours after IMP administration with vital signs taken every 30 minutes (±5 minutes) from the end of the saline flush or until stable, whichever is later (only applicable through Visit 12E). Beginning at Visit 13E, blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes). Vital signs will be documented in the electronic case report form (eCRF).

As with any antibody, allergic reactions to IMP administration are possible. The clinical criteria for defining anaphylaxis for this study are listed in Appendix III. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, etc., and medical equipment to treat acute anaphylactic reactions must be immediately available at the study sites, and study personnel should be trained to recognize and respond to anaphylaxis according to local guidelines.

If an anaphylactic reaction or a systemic hypersensitivity reaction occurs, a blood sample will be drawn from the patient as soon as possible after the event. For details see section 11.1.3.

7.3 Manufacturing, Packaging, Labelling, and Storage of IMP

The IMP(s) will be manufactured, packaged, labelled, released (by a qualified person [QP]), and distributed in accordance with the principles of *Good Manufacturing Practice* (GMP*)*, under the responsibility of Lundbeck.

The IMPs will be provided in single dose vials of 20 mL each as solution for infusion.

The wording on the labels will be in accordance with GMP regarding labelling and national and/or local regulatory requirements. If additional information is to be added when the IMP is dispensed to the patients, this will be clearly stated on the labels, and the investigator will be instructed to do so.

No manipulation, repackaging, or relabeling of IMP is permitted after QP release by Lundbeck, unless a repackaging/relabeling agreement exists, and the documentation is available to Clinical Supply, Lundbeck, and, where necessary, new QP releases are made.

The IMP(s) will be identified using a unique medication number.

The IMPs must be stored in a safe and secure location, and in accordance with the storage conditions specified on the labels.

7.4 Method of Assigning Patients to Treatment

IRT will be used in this study. Each patient will be assigned a screening number by the IRT, and that number will be used to identify the patient throughout the study. When a patient is to be randomized, the investigator or a designated, unblinded site staff will use the IRT. The IRT allocates the patient to a treatment group and assigns the patient a randomization number in accordance with the specifications from Biostatistics, Lundbeck.

Randomization will take place at Visit 2 after confirmation that the participant continues to meet the inclusion/exclusion criteria. Patients will be randomized 2:1 to receive either study drug or placebo.

Stratification will be performed according to two factors, that is, CCI [redacted] CCI [redacted] and Region (US/Japan, with a maximum of 25% of patients from Japan). Patients with no available CCI [redacted] will be randomized into a third group labelled “missing”.

In the optional OLE period, all patients will receive Lu AF82422.

7.5 IMP Accountability

IMP accountability is documented in the IRT and using IMP forms.

The investigator and the designated, unblinded site staff must agree to only dispense IMP to patients randomized in the study. The designated, unblinded site staff must maintain an adequate record of the receipt and distribution of the IMP(s). This record must be available for inspection at any time.

7.6 Unblinding Procedures

Global Patient Safety, H. Lundbeck A/S, and the designated, unblinded site staff will have access to the unblinded information for the double-blind treatment for each patient. Access to these details will be via IRT.

Lu AF82422 is eliminated through proteolytic degradation and not metabolized through CYP P450 enzymes, thus no drug-drug interactions are expected and treatment with Lu AF82422 would not prevent any acute medical or surgical intervention.

The investigator may only break the code for a patient if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, if the investigator needs medical guidance, the investigator should consult the clinical research associate (CRA) and/or in some cases the medical monitor before breaking the code. The investigator must record the date and reason for breaking the code. If the emergency situation was an adverse event, it must be recorded on an *Adverse Event Form*. The CRA and the medical monitor must be notified immediately. The IRT will capture the date and time of the code break call. Information on the allocated treatment will be provided during the call and by email. When the code is broken for a patient, the patient must be immediately withdrawn from the study. If this occurs during a visit, the investigator must complete the visit as a Withdrawal Visit; otherwise, the patient will be asked to attend a Withdrawal Visit.

7.7 Post-study Access to IMP(s)

Post-study access to the IMP will not be available. Patients in the study will have access to appropriate medical care after they complete or withdraw from the study.

8 Concomitant Medication

8.1 Concomitant Medication

Concomitant medication is any medication other than the IMP that is taken during the study, from 3 months prior to Screening Visit up until the Safety Follow-up Visit.

The concomitant medications that are disallowed or allowed with restrictions during the study are summarized in Appendix II.

Details of all concomitant medications (prescription and over-the-counter) taken <3 month(s) prior to the Screening Visit must be recorded in the eCRF at the first visit. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit. If medically necessary, initiation of or change of dose of concomitant medication is allowed per investigator discretion.

Any new concomitant treatment should not be initiated the same day as a visit with IMP infusion, unless for immediate treatment of a drug reaction or in case of an emergency.

For any concomitant medication for which the dose was increased due to worsening of a concurrent disorder after enrolment in the study, the worsening of the disorder must be recorded as an adverse event (see section 11.1.1).

For any concomitant medication initiated due to a new disorder after enrolment in the study, the disorder must be recorded as an adverse event.

8.2 COVID-19 Vaccination

There is currently no data indicating that Lu AF82422 may interact with or impair the body's immunological response to the COVID-19 vaccines. Hence, there are no indications for safety concerns of concomitant use of the COVID-19 vaccines with Lu AF82422. As such, COVID-19 vaccination is allowed during this study with the guidance measures as described below.

The patient should not receive a COVID-19 vaccination (or any concomitant medication, see section 8.1) the same day as an IMP infusion. If the patient has recently received a COVID-19 vaccine, the investigator should judge if the patient can be administered the IMP infusion at the scheduled visit based upon the patient´s individual response to the COVID-19 vaccine.

In the current study, if a patient is administered a COVID-19 vaccine, this should be captured as concomitant medication in the eCRF, including the date that the vaccine was given. The name of the manufacturer and, if applicable, whether it was the "first, second or booster, etc." vaccination should also be added, in a bracket.

All adverse events, including those judged by the investigator to be related to the COVID-19 vaccine must be captured in the eCRF on the *Adverse Event Form*. A causality assessment, including an alternative causality as relevant, must be provided on the *Adverse Event Form*.

9 Study Visit Plan

9.1 Overview

The study concept components are presented in Panel 1 and the patient flow is also presented in Panel 1. An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 2and Panel 3. Further details are in section 10.

After completing or withdrawing from the study, the patient must be treated in accordance with usual clinical practice.

The study includes the following periods:

- Screening Period (4 weeks)
- Randomization Period (2 weeks)
- DBP (48 weeks to 72 weeks)
- Optional OLE (96 weeks)
- Safety Follow-up Period (20 weeks after last IMP administration)

9.2 Screening Period

9.2.1 Screening Visit (Visit 1, -6 Week)

Informed consent must be obtained before any study-related procedures are initiated, including washout of disallowed medications. At the US sites, the patients undergoing the additional objective censor-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 Screening Period will occur up to 4 weeks prior to randomization at Visit 2 and have a duration of approximately 4 weeks.

The main procedures performed at screening include signing the informed consent, demographics, diagnosis of MSA-P or MSA-C according to the Gilman criteria, MoCA, relevant history (medical, psychiatric, neurological, family history of MSA), concomitant medication MRI scan for eligibility and, in addition, evidence of MRI abnormalities supporting the diagnosis of MSA, physical and neurological examination, checking inclusion/exclusion criteria, UMSARS score, safety laboratory and other safety assessments. The Screening Visit can be performed over 2 days during the first week of the Screening Period. The MRI scan should be uploaded for central reading no later than 10 calendar days before the Randomization Visit.

All screening procedures are summarized in Panel 2. Assessments are described in detail in section 10.

9.2.1.1 Patient Identification Card

Each patient will be provided with a patient identification card that states, at a minimum, the name of the IMP, the study number, the patient identification number, and the investigator's name and contact information.

The patient identification card should be returned to the investigator upon completion of the patient's participation in the study.

9.2.1.2 Re-screening

Re-screening is only allowed for patients who screen fail for administrative reasons, or who screen fail due to a change in concomitant medication allowed with restrictions within 8 weeks prior to randomization or have previously screen failed due to an eligibility criterion that has since been revised or removed. The patients must otherwise be eligible for the study at the time of screen failure. Re-screened patients will receive a new screening number.

Authorization for re-screening may only be granted by the sponsor's medical expert (or the CRO's medical monitor) after a thorough review of all data from the original Screening Visit.

At the new Screening Visit, the patient and caregiver must sign a new *Informed Consent Form*. At the new Screening Visit, the patient will be assigned a new screening number. A re-screened patient must have an *entirely* new Screening Visit with all screening procedures and assessments performed again, except for the screening MRI scan if performed within the last 3 months. All the eligibility criteria must be re-assessed at the new Screening Visit.

The following information will also be recorded in the eCRF at the new Screening Visit:

- that the patient has previously been screened for the study
- that re-screening has been authorized (by the sponsor's medical expert OR state who)
- the screening number that was assigned to the patient at the original Screening Visit

If a patient is re-screened, no data from the original Screening Visit will be used except for the original screening MRI if not repeated.

A patient may only be re-screened once.

9.3 Randomization Period

See section 10.1.1.

9.4 Double-blind Period

9.4.1 Baseline Visit (Visit 3, Week 0)

Important procedures at baseline include MRI scan for volumetric and diffusivity measures, application of IMP PK measurement of IMP in blood and CSF, biobanking samples and pregnancy test. The full list of assessments at the Baseline Visit are summarized in Panel 2.

9.4.2 General Outline of Visits During Double-blind Period

During the DBP, site visits will be every 4 weeks ±3 days with the possibility of completing the assessments over a maximum of 2 consecutive days for a given visit; and if so, then the first day is considered the "Visit" day according to the schedule and at IMP Visits, the visit must be registered in IRT and IMP administered to the patient on the second day. In addition, two telephone visits (Visits 4 and 8) will be conducted during the DBP to record adverse events and concomitant medication.

9.4.3 End-of-Treatment Visit – Double-blind Period

The individual DBP will vary from 48 weeks up to 72 weeks. Once the last patient reaches 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 EoT Visit will have their next scheduled visit converted to an EoTDBP Visit with assessments as listed for Visit 24, as according to Panel 2.

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 (for example, Microsoft Teams). The Study Experience interview will be conducted within 6 weeks after the completed Exit interview for patients who consent.

Patients who do not consent to the optional OLE will enter the Safety Follow-up Period after the EoTDBP Visit.

9.4.4 Safety Follow-up Visit 20 Weeks After Last Dose of IMP – Double-blind Period

A Safety Follow-up is conducted to capture new adverse events that occur during the Safety Follow-up Period as well as to follow-up on the outcome of adverse events on-going at the end of the treatment period. In addition, the following will be collected; blood and urine samples for clinical safety laboratory tests, blood sampling for IMP quantification and anti-drug antibodies (ADAs), vital signs, physical and neurological examination, ECG, C-SSRS assessment, concomitant medication and pregnancy test. The Safety Follow-up Visit must be conducted as a visit to the site. The Safety Follow-up Visit is scheduled 20 weeks after the last dose of IMP.

For adverse events that were on-going at the EoTDBP or Withdrawal Visit and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse

events still on-going at the Safety Follow-up Visit, the *On-going Adverse Event* checkbox on the *Adverse Event Form* must be ticked. SAEs must be followed until resolution, or the outcome is known.

For details of assessments to be conducted at the Safety Follow-up Visit see Panel 2.

9.5 Optional Open-label Extension Period

Patients who consent to the optional OLE will enter the OLE under the circumstances defined in section 6.3.

Treatment with Lu AF82422 will continue on the first visit of the OLE (Visit 1E) which will take place at the same day as the EoTDBP Visit, or as soon as possible thereafter, but no later than 5 months after the EoTDBP Visit, and will be enrolled into the OLE no later than the end of Q1 2024. If a Safety Follow-up Visit for the DBP is due before the OLE is implemented, it should be completed per Panel 2. The patient could afterwards enter the OLE and treatment could continue for a planned period of 96 weeks. OLE procedures will be performed as presented in Panel 3.

For patients who enter the OLE and have the first visit of the OLE at the same day of the EoTDBP visit, clinical assessments would not have to be repeated. In that case, data will automatically be transferred. However, in case of >7 days in between the EoTDBP visit and the first visit of the OLE, clinical assessments would have to be re-performed.

9.5.1 End-of-Treatment Visit – Optional Open-label Extension Period

Patients who enter the OLE will receive the first open-label dose of Lu AF82422 (Visit 1E) on the same day as the EoTDBP or as soon as possible thereafter and the last dose on Visit 24E (Week 92E); EoT in the 96-week OLE is at Visit 25E (Week 96E).

9.5.2 Safety Follow-up Visit Open-label Extension Period 20 Weeks After Last Dose of IMP

A Safety Follow-up Visit of the extension period (SFU-E) is conducted to capture new adverse events that occur during the Safety Follow-up Period as well as to follow-up on the outcome of adverse events on-going at the end of the treatment period. In addition, the following will be collected; blood and urine samples for clinical safety laboratory tests, blood sampling for IMP quantification and ADA, vital signs, physical and neurological examination, C-SSRS assessment, concomitant medication and pregnancy test. The Safety Follow-up must be conducted as a visit to the site. The Safety Follow-up Visit is scheduled 20 weeks after the last dose of IMP.

For adverse events that were on-going at the EoTOLE, or Withdrawal Visit and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse events still on-going at the Safety Follow-up Visit, the *On-going Adverse Event* checkbox on

the *Adverse Event Form* must be ticked. SAEs must be followed until resolution, or the outcome is known.

The Safety Follow-up Visit for patients who withdraw consent must be performed, if at all possible; any information collected will only be recorded in the patients' medical records.

For details of assessments to be conducted at the Safety Follow-up Visit, see Panel 3.

9.6 Withdrawal Visit

Patients who withdraw from the study prior to the respective EoT Visit for the treatment period (ie, EoTDBP or EoTOLE) will be asked to attend a Withdrawal Visit and Safety Follow-up Visit, if at all possible. If the patient cannot attend the site physically for the Withdrawal Visit, and the visit would then not be performed, the visit should be performed as a remote or Telemedicine visit with assessments performed as described in the "COVID-19 Mitigation Plan", if possible. The Withdrawal Visit must be scheduled as soon as possible after withdrawal.

No new information will be collected from patients who withdraw from the study, except information collected in relation to the scheduled Withdrawal Visit and the Safety Follow-up Visit 20 weeks after last dose of IMP or needed for the follow-up of adverse events (section 11.5).

MRI scanning is only to be performed as an EoT/withdrawal procedure if it was not performed within the last 8 weeks.

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

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

The Exit interview will be conducted within 3 weeks after the Withdrawal Visit for patients who have been in the DBP for at least 48 weeks prior to withdrawal. For patients who withdraw from study treatment after Week 48 in the DBP and complete an Exit interview, patients may be contacted to participate in a Study Experience interview.

The reason for withdrawal must be recorded in the eCRF.

For a patient who withdraws consent:

- if the patient withdraws consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as the Withdrawal Visit and all the data collected up to and including that visit will be used.

- if the patient withdraws consent during a telephone conversation, the investigator will ask the patient if he or she will attend a Withdrawal Visits. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including these visits will be used
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical records
- if the patient explicitly requests that the patient's data collected from the time of withdrawal of consent onwards not be used, this will be respected.

It is planned to conduct the same assessments as for the EoT if the patient is withdrawn during the DBP (Visit 18, for list of assessments see Panel 2).

9.7 Unscheduled Visit

If needed, an unscheduled visit can be performed between Randomization and the Safety Follow-up Visit for any of the safety assessments:

- Blood and urine sampling for clinical safety laboratory tests
- Blood sampling for ADA
- Vital signs
- Weight
- Examinations (physical, neurological)
- ECG
- MRI scan for safety
- C-SSRS
- Serum total tryptase sample to evaluate baseline tryptase level in the event of an anaphylactic reaction or a systemic hypersensitivity reaction

Adverse events must always be collected at an unscheduled visit.

9.8 End-of-study Definition

The end of the study for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient on-going in the study.

10 Assessments

10.1 Screening and Baseline Procedures and Assessments

10.1.1 Randomization Visit (Visit 2, Week -2)

Randomization will be performed at Visit 2 after checking inclusion/exclusion criteria, as well as signs and symptoms present. The tablet to record falls (fall diary) and other patient-reported outcomes (PROs) will be handed out. All PROs will be administered electronically by using a tablet. The patients and their caregivers will be trained on how to use the electronic PROs (ePROS) by site staff who have adequate experience with MSA patients and have received adequate training on good standards in providing guidance to patients on how to use the ePROs.

In exceptional cases, the visit interval between the Screening and Randomization Visits may be extended with consent from the Lundbeck medical expert/medical monitor, provided the Lundbeck medical expert accepts the rationale provided for the extension. The full list of assessments at the Randomization Visit are summarized in Panel 2.

10.1.2 Demographics and Baseline Characteristics

Prior to enrolling a patient in the study, the investigator must ascertain that the patient meets the selection criteria. The following will be subject to assessment after the *Informed Consent Form* has been signed:

- Diagnosis (see diagnostic assessment in section 10.1.3)
- MSA History (onset of motor and/or autonomic MSA symptoms, date of MSA diagnosis, blood relatives with diagnosis of MSA)
- MoCA
- Recent and on-going medication
- Medical history
- Demographics (age, sex, race)
- Height and weight
- Signs and symptoms; adverse events
- MRI for eligibility and, in addition, presence of MRI abnormalities supporting the diagnosis of MSA
- UMSARS for eligibility
- Blood sampling for NfL

Safety at screening

- Physical and neurological examination
- Vital signs
- ECG
- C-SSRS
- Blood sampling for pregnancy test
- Blood and urine sampling for clinical safety laboratory tests (as listed in Panel 2, Panel 3, and Panel 5)

10.1.2.1 Montreal Cognitive Assessment (MoCA)

MoCA is a cognitive test (available at https://www.mocatest.org) assessing 8 cognitive domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation (place and time). Normal score would be ≥26/30 achievable points. Inclusion criterion is ≥22 points at screening.

10.1.3 Diagnostic Assessments

The following diagnostic assessments will be performed:

- Diagnosis (possible or probable MSA-P or MSA-C according to the Gilman criteria)
- Inclusion/exclusion criteria pertaining to diagnosis and prognosis (see section 6.3)
- Relevant history (medical, psychiatric, neurological, family history of MSA)
- Physical and neurological examination
- MRI scan

10.2 Efficacy Assessments

10.2.1 Clinical Outcome Assessments (COA)

10.2.1.1 Use of COA Tools

The following COA tools will be used for efficacy assessment:

- UMSARS – to assess the severity of MSA symptoms, impacts, and disease progression
- Composite Autonomic Symptom Scale (COMPASS) Select (Baseline) and COMPASS Select Change (subsequent visits) – to assess severity of autonomic symptoms
- Schwab and England Activities of Daily Living (SE-ADL) – to assess function, level of dependency
- Clinical Global Impression – Severity (CGI-S) – to assess clinical global impression of MSA severity
- Patient Global Impression – Severity (PGI-S) – to assess patient global impression of MSA severity

- Observer-reported Global Impression - Severity of Illness (OGI-S) – to assess caregiver observed global impression of MSA severity in the patient
- Fall eDiary – to assess fall events and consequences of falls
- FeetMe® – to assess gait parameters (in a subset of patients in the US)
- PAMSys – to assess frequency of falls (in a subset of patients in the US)

Detailed instructions on how to administer the COA tools and how to score using them will be provided to the site in *Rater Guideline and Vendor Manuals*.

Rater training of electronic COA as well as central review of UMSARS Part I and Part II will be provided by MedAvante-Prophase.[1] Central review will only be performed during DBP. Training materials are available throughout the duration of the study on the training provider's eLearning platform, which can be accessed from any device. Independent Review Guidelines, as well as Videography training modules, are part of the training provider's eLearning platform and are accessible the same way as COA training.

The UMSARS, COMPASS-S/SC, SE-ADL, CGI-S, PGI-S, OGI-S, and Fall eDiary will be administered in the local language. Only those provided by Lundbeck that have been validated in the language to which they have been translated will be used in this study.

The COMPASS-S/SC, PGI-S and Fall eDiary are PROs: guidance will be provided to patients on how to complete them and how to use the ePRO device.

The OGI-S is a carer/observer-reported outcome: guidance will be provided to caregivers on how to complete the scale and how to use the electronic outcome device.

10.2.1.2 Unified Multiple System Atrophy Rating Scale (UMSARS)

The UMSARS is a combined clinician and patient-reported scale to assess motor impairment in MSA patients.[10] The UMSARS consists of four parts:

Part I assesses historical information on symptoms and activities of daily living over the past 2 weeks as reported by patients and caregivers (12 items) rated on a scale ranging from 0 = not affected to 4 = unable to do the activity (Note; each item uses different anchor descriptors as relevant to the question addressed).

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

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

[1] MedAvante-Prophase is now part of WCGclinical.com

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

The total UMSARS score (UMSARS TS) is obtained by the sum of the items from Part I and Part II. Part I scores range between 0 to 48, and Part II scores range between 0 and 56. A higher score indicates greater impairment. An experienced neurologist can use the UMSARS after a short training session. It takes approximately 30 to 45 minutes to administer the UMSARS. The administration of UMSARS Part I and Part II will be video recorded for central reading.

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

The abbreviated UMSARS (aUMSARS) score is derived from a subset of items from UMSARS Part I and Part II shown to be patient centric and sensitive to progression in MSA. Thus, the UMSARS will be administered only once to the patient (according to standard procedures) at the clinic visit to derive the UMSARS TS, mUMSARS and abbreviated scores.

The aUMSARS has been developed to be patient centric (relevant to patients) and sensitive to detect change in patients diagnosed with possible and probable MSA. The abbreviated UMSARS score will be derived by a subset of items from Part I and Part II in the original UMSARS scale. The clinician will administer the full original UMSARS to assess MSA signs and symptoms and its impact on function. Raters will be kept blinded to the items constituting the abbreviated UMSARS to avoid bias during patient examination. Full details on how to generate the abbreviated UMSARS score will be described in the 18331A Statistical Analysis Plan (SAP).

Central reading of the UMSARS scale during the DBP will be provided by the vendor (MedAvante-Prophase).

10.2.1.3 Composite Autonomic Symptom Scale – Select and Select Change (COMPASS-S/SC)

The COMPASS Select,[15] a patient-reported scale, consists of a subset of 36 items derived from the original COMPASS,[16] to assess severity of autonomic symptoms in MSA during the last year. The COMPASS Select includes 3 domains related to blood pressure control: syncope, orthostatic intolerance, and vasomotor symptoms; and 3 domains focused on symptoms of disturbed secretomotor, bladder, and sleep function.

The COMPASS Select Change is a derivate of COMPASS Select, consisting of 16 items in which patients are asked to score their change in autonomic symptoms since their last visit. The scoring algorithm of COMPASS is highly complicated and requires computer analysis for score generation. A higher score indicates greater autonomic symptom severity. It takes approximately 10 to 15 minutes to complete the COMPASS-S and COMPASS-SC.

10.2.1.4 Schwab and England Activities of Daily Living (SE-ADL)

The SE-ADL is a combined patient- and clinician-reported scale to assess patients physical functioning in activities in daily living to grade functional status.[11] For the 18331A study only the clinician-rated part will be administered. The SE-ADL rates the patient's function on a scale ranging from 0% indicating worst possible function to 100% indicating no impairment. Each 10-point increment is accompanied by a description of function. The score is obtained by the 10-point response option applicable for the patient. The SE-ADL can be administered by an experienced health care professional after a short training. It takes approximately 5 to 10 minutes to rate the SE-ADL.

10.2.1.5 Clinical Global Impression-Severity of Illness (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 at the time of assessment. 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).

10.2.1.6 Patient Global Impression – Severity of Illness (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.

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

The OGI-S is a 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.

10.2.1.8 MSA Fall Diary

At the Randomization Visit, all patients will be provisioned and trained on an electronic MSA Fall Diary. During the study patients will be instructed to record fall events on a daily basis using a MSA Fall Diary during 5 distinct intervals; 2 weeks between Randomization Visit and Baseline Visit and 4 intervals of 4 weeks during the DBP. Patients are asked to report date/time of falls (yes/no), location of the fall (indoors or outdoors, familiar or unfamiliar environment), cause of fall (experience of orthostatic symptoms or freezing of gait), action

taken, and type of injury sustained (if any). At the end of each week patients will also be asked to report any health care professional visits and hospital visits and type of examination (for example, X-ray due to the fall etc.). The use of the fall diary 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 to be dispensed.

10.2.1.9 FeetMe®

At US sites, additional, objective sensor-based assessments will be performed during 5 distinct intervals (2 weeks interval between randomization and baseline, then 4 periods of 4 weeks) on consenting subsets of patients in the US (hereafter referred to as the "Sensor subset"). Patients can withdraw from these additional assessments without having to withdraw from the main study. Patients may consent to participate in one or both of the objective sensor-based assessments. 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.

FeetMe® solution includes connected insoles FeetMe® Insole, FeetMe® Evaluation mobile application and FeetMe® Mobility web platform. FeetMe® Insole combines pressure sensors, motion sensors and embedded calculation power, which allow to calculate more than 20 gait metrics for every step. The patients receive insoles during scheduled visits and are asked to wear the insoles continuously for 10 days in their home environment.

Metrics calculated for every step with FeetMe® Insole:

- Stride length
- Walking speed
- Width motion
- Cadence
- Stride time
- Single support time
- Swing time
- Double support time
- Pressure distribution
- Stride length difference
- Strides time difference
- Distance travelled
- Support asymmetry
- Trajectory centre of pressure

Detailed instructions on how to administer FeetMe® digital insoles will be provided to the site in a Rater Guideline.

10.2.1.10 PAMSys

At US sites, patients will have the option for undergoing objective sensor-based assessments, which will be performed during 5 distinct intervals (2 weeks interval between randomization and baseline, then 4 periods of 4 weeks) (hereafter referred to as the "Sensor subset"). Patients can withdraw from these additional assessments without having to withdraw from the main study. Patients may consent to participate in one or both of the objective sensor-based assessments. The use of the sensor 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 sensor is to be dispensed.

BioSensics' PAMSys is a system that consists of a wearable motion sensor that is paired to a tablet. The wearable sensor is worn as a pendant on the chest for continuous monitoring of falls and physical activity. The tablet supports electronic COA technology, which, when a fall is detected by a sensor, asks the patient to confirm or deny the occurrence of the detected fall. Patients receive the sensor during the scheduled visits and are instructed to wear the sensor continuously for 30 days at each interval and bring the sensor back at the next scheduled visit.

The parameters provided by the PAMSys system are: number of detected falls, posture classification (sitting, standing, walking and lying down), number of steps, and compliance for wearing the sensor.

Detailed instructions on how to administer PAMSys system will be provided to the site in a Rater Guideline.

10.2.1.11 Rater Qualification

Rater training and certification will be conducted by the MedAvante-Prophase who will also provide training, including the video recording and central review process (as agreed with the sponsor). Raters will complete their designated training curriculum based on their initial qualification status and assigned role. The training programme will also include instructions on general COA administration, quality assurance and management guidance.

The UMSARS and the CGI-S, should only be administered by a rater having adequate experience with MSA and administration of semi-structured interviews. The rater should be a clinician, such as a neurologist, involved in clinical practice or regularly evaluating MSA patients. SE-ADL can be administered by a health care professional with adequate experience with MSA and administration of semi-structured interviews. Any exceptions must be discussed and approved by Lundbeck and/or its designee. All clinician-reported outcomes will be administered electronically by using a site tablet. For each scale, the same rater should preferably rate the same patient throughout the study.

All PROs will be administered electronically by using a tablet. The patients will be trained on how to use the ePROs by site staff who have adequate experience with MSA patients and have received adequate training on good standards in providing guidance to patients on how to use the ePROs. Any exceptions must be discussed and approved by Lundbeck and/or its designee.

Only site staff who have received adequate training on good standards in administering the COMPASS-S/SC, PGI-S and MSA Fall Diary, and how to use the FeetMe® and PAMSys, digital devices will be authorized to train the patients on completion of ePROs and the use of digital devices in the study. Documentation of training will be provided to site staff for archiving in the investigator trial master file (TMF).

New electronic COA and digital device trainers joining the study must be trained similarly. Rater training of electronic COA will be provided by MedAvante-Prophase.

Only raters who qualify on study-specific Rater Certification Programme will be authorized to administer and rate the COAs in the study. Documentation of training and certification will be provided to raters for archiving in the investigator TMF. No patient must be rated before the documentation has been archived.

New raters joining the study will be trained and certified by using the same certification process.

For each individual patient, the same certified rater should preferably rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study.

10.2.1.12 External COA Monitoring Oversight

Lundbeck reserves the right to use external quality oversight methods to ensure eDiary compliance and COA data quality (as well as ensure accurate administration of the COAs). For this study, the CRO will conduct the external data monitoring (to be agreed with the sponsor) which will include the following quality oversight methods:

- Compliance check (that is, MSA Fall Diary)
- Independent review of source documents
- Clinical data analytics review

10.2.2 Imaging Assessments

10.2.2.1 Imaging Procedures

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.

MRI scans will be performed for evaluation of biomarkers of disease progression and safety. Patients must visit designated imaging facilities for the MRI scans. The scans will be evaluated by a central reader, as pre-specified in the study-specific *Imaging Charter*. A study-specific *Imaging Manual*, detailing procedures for scan acquisition, will be issued to all participating imaging centres.

The following assessments will be performed for evaluation of disease progression:

- Volumetric MRI (vMRI) for quantification of atrophy measures in brain regionsofinterest (ROIs) (for example, caudate nucleus, putamen, striatum, pons, brain stem, and cerebellum)

The following assessment will be performed, where available, for evaluation of disease progression in DBP:

- Diffusion-tensor imaging (DTI) for quantification of diffusivity measures in brain ROIs (for example, caudate nucleus, putamen, globus pallidus, pons, cerebellar white matter, and middle cerebellar peduncle)
- Arterial spin label (ASL) for quantification of cerebral blood flow (CBF) in selected brain regions (for example, putamen and cerebellum)

Additional MRI sequences will be performed for assessment of safety in DBP, 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.

10.2.3 Biomarker Assessments

MRI biomarkers are included as secondary and exploratory endpoints to investigate if the delay in clinical progression is supported by a delay in the underlying neuropathological process (section 10.2.2).

The inclusion of blood and CSF biomarkers as exploratory endpoints will allow the understanding of any downstream biomarker effects of potential α-synuclein reduction and the establishment of a clear link between biomarker and clinical endpoints (section 10.4).

Blood Biomarkers:

- NfL concentrations
- plasma concentrations of “free” and “total” α-synuclein

CSF Biomarkers:

- t-tau and NfL concentrations
- concentrations of “free” and “total” α-synuclein
- pathological species of α-synuclein

10.2.3.1 NfL and t-tau Analysis

The blood for the analysis of NfL and CSF for analysis of NfL and t-tau will be drawn in accordance with Panel 2 and Panel 3. CSF sampling will not be applicable for patients with contraindications of lumbar puncture, 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, in the opinion of the investigator that would preclude CSF collection. The blood and CSF sampling and handling procedures are described in the *Laboratory Specification Manual*.

The analysis will be performed by vendors with a validated assay, under the responsibility of H. Lundbeck A/S.

10.3 Quality of Life Assessments

The following COA tools will be used for quality of life assessment:

- EuroQol 5-Dimensions, 5 Levels (EQ-5D-5L)

10.3.1 EuroQol 5-Dimensions, 5 Levels (EQ-5D-5L)

The EQ-5D-5L[17] is a patient-reported assessment designed to measure the patient's wellbeing. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 5-point index ranging from 1 (no problems) to 5 (extreme problems) and a single summary index (from 0 to 1) can be calculated. The VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ-5D-5L can be administered by a study nurse after a brief training. It takes approximately 5 minutes to complete the EQ-5D-5L.

10.4 Pharmacokinetic Assessments

Blood and CSF sampling for PK evaluation will target quantification of "free" (that is, not bound to α-synuclein) Lu AF82422 in plasma and CSF.

PK in plasma: At baseline, Weeks 12 and 36, multiple plasma PK samples are to be taken relative to IMP infusion: before infusion, immediately after the EOI, 1 and 2 hours after EOI. At the other visits with PK sampling, PK samples will be sampled before IMP administration. The blood sampling and handling procedures are described in the *Laboratory Specification Manual*. PK assessments will be performed in blood plasma according to the schedule depicted in Panel 2 and Panel 3.

PK in CSF: CSF sampling will not be applicable for patients with contraindications of lumbar puncture, 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, in the opinion of the investigator that would preclude CSF collection. The blood sampling and handling procedures are described in the *Laboratory Specification Manual*. Pharmacokinetic assessments will be performed in CSF according to the schedule depicted in Panel 2.

The samples will be analyzed using a validated bioanalytical method by a bioanalytical laboratory under the responsibility of sponsor. Analysis method will be defined in a Bioanalytical Protocol and be reported in a Bioanalytical Report.

10.5 Target Engagement Assessments

The following parameters will be assessed:

- Blood sampling for α-synuclein; for quantification of "free" and "total" α-synuclein in plasma
- CSF sampling for α-synuclein; for quantification of "free", and "total" α-synuclein
- CSF sampling for pathological species of α-synuclein; for example, aggregated and truncated. The blood and CSF samples for analysis of "free" and "total" α-synuclein as well as pathological species in CSF will be drawn as shown in Panel 2 and Panel 3. The blood sampling and handling procedures are described in the *Laboratory Specification Manual*.

For the site, all samples will be sent to ICON Central Labs and ICON Central Labs will manage the onward distribution to the Special Laboratories. The samples will be analyzed using a scientific validated bioanalytical method by a bioanalytical laboratory under the responsibility of sponsor. Analysis method and samples analysis will be reported in a separate report.

10.6 Safety Assessments

10.6.1 Adverse Events

The patients will be asked a non-leading question (for example, "how do you feel?", "how have you felt since your last visit?") at each visit, starting at the Screening Visit when the patient signs the *Informed Consent Form*. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by the patient will be recorded, and the investigator will assess the seriousness and the intensity of each adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, MRI, C-SSRS, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See section 11 for further information on adverse events.

10.6.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 5.

Panel 5 Clinical Safety Laboratory Tests

Haematology	**Liver**[b]	**Urine**
B-haemoglobin B-erythrocyte count B-total leucocyte count B-neutrophils[a] B-eosinophils[a] B-basophils[a] B-lymphocytes[a] B-monocytes[a] B-thrombocyte count B-haematocrit P-prothrombin time S-total tryptase[d]	S-total bilirubin S-conjugated bilirubin S-alkaline phosphatase S-alanine aminotransferase S-aspartate aminotransferase S-gamma-glutamyl transferase	U-protein (dipstick) U-glucose (dipstick) U-blood (dipstick) U-leucocytes (dipstick) U-nitrites (dipstick) Urine culture
Electrolytes[b]	**Kidney**[b]	**Infection**
S-sodium S-potassium S-calcium (total)	S-creatinine S-urea nitrogen	S-C-reactive protein
Endocrine and Metabolic[b]	**Lipids**[b]	**Pregnancy**[c]
S-albumin B-HbA_{1c} S-creatine phosphokinase	S-low density lipoprotein S-high density lipoprotein S-triglycerides S-cholesterol (total)	hCG tests
B = blood; hCG = human choriogonadotropin; P = plasma; S = serum; U = urine		

a Count and % of total leucocytes. If any abnormalities are noted in the complete blood count and/or differential counts, additional workup (ancillary tests) will be performed

b Clinical chemistry

c Only for women of childbearing potential, serum hCG test at screening and urine dipstick at later assessments

d S-total tryptase only to be collected in relation to systemic hypersensitivity reactions (adverse events requiring additional data collection), see section 11.1.3

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 2 and Panel 3. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analyzed at the central laboratory.

The investigator must review (initial and date) the results of the clinical safety laboratory tests as soon as possible after receipt of those results. Out-of-range values must be interpreted by the investigator as “not clinically significant” or “clinically significant” with a comment concerning the planned follow-up. Tests for clinically significant out-of-range values must be repeated, or an appropriate clinical follow-up must be arranged by the investigator and documented on the laboratory report, until the value has stabilized or until the value has returned to a clinically acceptable value (regardless of relationship to the IMP). A patient with a value that is out-of-range at an EoT or Withdrawal Visit and considered clinically significant must be followed in accordance with usual clinical practice.

If the clinically significant out-of-range clinical safety laboratory test value has not normalized or stabilized or a diagnosis or a reasonable explanation has not been established by the DBP/OLE Safety Follow-up Visit, the investigator must decide whether further follow-up visits are required (this may include an additional medical examination and/or additional blood sampling). Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical records.

For patients that attend the DBP Safety Follow-up Visit before entering the OLE:

Clinically significant out-of-range clinical safety laboratory test values that have not normalized or stabilized or a diagnosis or a reasonable explanation has not been established by the DBP Safety Follow-up Visit should be followed-up on in the OLE by the investigator in accordance with the above.

General

Any out-of-range clinical safety laboratory test value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

The central laboratory will be notified by the sponsor when the biological samples may be destroyed.

10.6.3 Vital Signs

The investigator may appoint a designee to measure vital signs, provided this is permitted according to local regulations and provided the investigator has trained the designee how to measure vital signs. The investigator must take responsibility for reviewing the findings.

Pulse rate and blood pressure will be measured using a standard digital meter in either supine or sitting position immediately prior to start of IMP administration.

Blood pressure and pulse will be measured immediately prior to IMP administration and patients will be monitored immediately after IMP administration inclusive of saline flush (±5 minutes) for immediate drug reactions for a minimum of 2 hours with vital signs taken at the end of the saline flush and then every 30 minutes (±5 minutes) from the end of the saline flush or until stable, whichever is later (applicable only through Visit 12E).

Beginning at Visit 13E, blood pressure and pulse will only be measured immediately prior to and immediately after IMP administration, inclusive of the saline flush (±5 minutes).

Any out-of-range vital sign considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form* as according to section 11.1.1.

10.6.4 Height and Weight

The patient's height will be measured at screening only.

The patient's weight will be measured while wearing light clothing and no shoes.

10.6.5 Electrocardiograms

A standard 12-lead ECG will be recorded using digital ECG recording equipment provided to the investigator or, upon agreement, to an external cardiology centre. The ECGs will be transferred digitally to a central ECG laboratory for evaluation. The investigator will be provided with the results and a cardiological interpretation of the ECG from the central ECG laboratory. Still, the investigator should examine the ECG according to his own judgement for any safety concerns.

The results from the central ECG laboratory will include the RR, PR, QRS, QT, and QT_c intervals.

The investigator has the final decision on the interpretation of the ECG results, except for determining exclusion criteria at screening (PR, QRS, and QT interval described in Exclusion Criterion 22 in section 6.3).

Any abnormal ECG result or out-of-range ECG parameter value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

10.6.6 Physical and Neurological Examinations

The investigator may appoint a designee to be primarily responsible for performing the physical examinations, provided this is permitted according to local regulations. The investigator must take responsibility for reviewing the findings. Whenever possible, the same individual should perform all physical examinations for the patient.

The physical examination (including height at the Screening Visit only) must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen, and musculoskeletal system and must be performed by a physician or physician assistant. The examination will include recording of use of feeding tube and/or wheelchair (full-time user – no walking ability; occasional user – limited walking ability).

Genito-urinary system examinations are often not part of routine neurologic practice. For most patients, an external inspection of the genitals should be sufficient. A full gynaecological examination should only be performed if warranted by symptoms or medical history. The renal regions will be examined as part of the abdominal examination.

The neurological examination must be performed by a physician. The neurological examination comprises examination of mental status, cranial nerves, motor system, reflexes, sensory system, coordination, station and gait.

Any abnormal finding or out-of-range value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form.*

10.6.7 Columbia-Suicide Severity Rating Scale

The C-SSRS[18] is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study. The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of ideation, and 4 questions addressing suicidal behaviour. For this study, the following versions of the scale are used: the "Baseline/ Screening" version (lifetime and 6 months assessment) and the "Since last visit" version (for all subsequent visits). It takes approximately 5 to 10 minutes to administer and rate the C-SSRS.

The C-SSRS must be administered in the local language.

The C-SSRS should only be administered by a rater who has adequate experience with clinical studies in CNS indications. The rater should be a clinician, such as a neurologist, geriatrician, psychiatrist, (neuro-) psychologist, or study nurse involved in clinical practice or regularly evaluating patients. For each individual patient, the same certified rater should preferably rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study. Any exceptions must be discussed and approved by Lundbeck and/or its designee.

Rater training and certification will be conducted by the MedAvante-Prophase as agreed with the sponsor. Raters will complete their designated training curriculum based on their initial qualification status and assigned role. Only raters who qualify on study-specific Rater Certification Programme will be authorized to administer the C-SSRS in the study. C-SSRS rater certification will be provided by Kelly Posner online training. Documentation of training and certification will be provided to raters for archiving in the investigator TMF. No patient must be rated before the documentation has been archived. New raters joining the study must be trained and certified by using the same certification process. Detailed instructions on how to administer the C-SSRS will be provided to the site in a C-SSRS Guideline.

Any finding on the C-SSRS that is considered clinically significant by the investigator should be reported as an adverse event.

10.6.8 Anti-drug Antibody Assessments

The plasma samples for ADA quantification in plasma will be drawn in accordance with Panel 2 and Panel 3.

The blood sampling and handling procedures are described in the *Laboratory Specification Manual*. In total, 8.0 mL are needed for all ADA assays in plasma.

Plasma samples will be analyzed to determine presence or absence of ADA. Samples confirmed positive for ADA will be evaluated for clearing ADAs by evaluation of exposure and TE.

The plasma samples will be analyzed for anti-Lu AF82422 antibodies using a bioanalytical method validated for screening, confirmation and titration.

The samples will be analyzed using a validated bioanalytical method by a bioanalytical laboratory under the responsibility of sponsor. Analysis method and samples analysis will be reported in a separate report.

10.6.9 Other Safety Assessments

All MRI scans during the DBP will be analyzed for safety assessments, especially evaluation of clinically important findings for example, microhaemorrhages, infarcts and meningoencephalitis. Details on MRI findings are specified in the *Imaging Charter*. Principal investigator provides assessment of MRI result.

Clinically significant MRI changes to be reported as adverse event.

10.7 Other Assessments

The following other assessments are performed:

- Exit Interviews (in all patients in the US; note that the caregivers participate in this assessment as in UMSARS and OGI-S scores)
- Study Experience Interviews (in a subset of patients in the US; note that the caregivers participate in this assessment)

10.7.1 Exit Interviews

At US sites, semi-structured, qualitative interviews will be performed in the Exit Interview subset (to be detailed in a separate interview protocol) on consenting subsets of patients and caregivers (hereafter referred to as “Exit Interview subset”). Patients and caregivers from the Exit Interview subset will participate in an Exit interview within 3 weeks after the EoTDBP Visit or within 3 weeks after the DBP Withdrawal Visit. For patients withdrawing from the study, the Exit interview will only be performed if they have been in the DBP for at least 48 weeks.

Interviews will be conducted over the phone by trained third-party interviewers following dedicated semi-structured interview guides. Each individual interview will last about 45 minutes with the patients and about 60 minutes with the caregivers.

Interviews will be audio-recorded and then transcribed verbatim. Transcripts will be de-identified and considered source documents.

The patients and caregivers may also withdraw from the interviews without having to withdraw from the main study.

Details on recording and reporting of adverse events/SAEs from the Exit interviews are described in the separate interview protocol.

10.7.2 Study Experience Interviews

At US sites, patients and caregivers may be contacted to participate in a semi-structured, qualitative interview (to be detailed in a separate interview protocol) with consenting subsets of patients and caregivers (hereafter referred to as "Study Experience Interview subset"). The interview will focus on the overall study experience, including topics such as logistical considerations, satisfaction with participation in the study, and suggestions for improvement for future studies. Interviews will be conducted within 6 weeks after completion of the Exit interview.

Interviews will be conducted by web conferencing platform (for example, Microsoft Teams) or by telephone, by trained third-party interviewers following dedicated semi-structured interview guides. Each individual interview will last about 30 minutes with the patients and about 30 minutes with the caregivers.

Interviews will be audio-recorded and then transcribed verbatim. Transcripts will be de-identified and considered source documents.

The patients and caregivers may also withdraw from the interviews without having to withdraw from the main study.

Details on recording and reporting of adverse events/SAEs from the Study Experience interviews are described in the separate interview protocol.

10.8 Biobanking

10.8.1 General Considerations

Although the potential future exploratory biomarker analyses will help to increase our understanding of the aetiology of disease and the molecular basis of the drug response, the efforts described in this protocol are strictly research based. Therefore, as the complex interactions between genes and disease are currently not characterized to a level that translates to a meaningful clinical advantage, individual results from the exploratory biomarker analyses will not be given to the patients. For the same reasons, individual results will not be added to the patients' medical records.

The patients will have no direct benefit from the exploratory biomarker analyses.

The blood samples for gene expression profiling (RNA), metabolomics/proteomics (plasma), pharmacogenetics (DNA) (optional), ADA, and CSF sampling analysis will be single-coded using the patient's screening number. The blood samples for genetic biomarker analysis will be single-coded using the patient's screening number.

10.8.2 Blood Sampling for Gene Expression Profiling (RNA)

Blood samples (approximately 5.0 mL per sample) for gene expression profiling (RNA) will be collected in PAXgene RNA tubes in accordance with Panel 2.

The blood sampling and handling procedures are described in the Laboratory Manual. The maximum volume of blood to be collected during the study for this purpose will be approximately 15 mL.

Samples for gene expression profiling will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, US) for storage.

The samples and any derived material will be destroyed ≤10 years after the end of the study.

10.8.3 Blood Sampling for Metabolomics and/or Proteomics

Blood sample for plasma separation and metabolomics/proteomics biomarkers analysis will be collected in one 10 mL K2 EDTA (ethylenediaminetetraacetic acid) tube in accordance with Panel 2. The blood sampling and handling procedures are described in the Laboratory Manual.

The maximum volume of blood to be collected during the study for this purpose will be approximately 30 mL. The plasma samples for metabolomics/proteomics biomarkers will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, US) for storage.

The samples and any derived material will be destroyed ≤10 years after the end of the study

10.8.4 Blood Sampling for Pharmacogenetics

Sampling for pharmacogenetics is optional and a separate signed informed consent must be in place to cover this analysis.

Blood samples (approximately 6 mL) for subsequent DNA extraction will be collected in K3 EDTA tube in accordance with Panel 2. The blood sampling and handling procedures are described in the Laboratory Manual.

The blood sample will be shipped to ICON central laboratory where DNA will be extracted and retained. DNA aliquots will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, US) for storage.

The genetic variants to be analyzed may include single nucleotide polymorphism (SNPs) and copy number variations (CNVs). The analytical methods may be polymerase chain reaction (PCR), qPCR (quantitative PCR), sequencing, or whole genome scans on microarrays.

The samples and any derived material will be destroyed ≤15 years after the end of the study.

10.8.5 Blood Sampling for Anti-drug Antibody

Additional to the ADA safety assessments described in section 10.6.8, ADA samples taken according to Panel 2 and Panel 3 will be shipped to Lundbeck Biobank (at Azenta Life Sciences, Indianapolis, IN, USA) for storage.

10.8.6 CSF Sampling for Proteomics and Genomics

CSF samples (approximately 10 mL) for subsequent experiments will be collected in a specified sampling tube.

Different proteins, aggregates or post-translational modifications may be analyzed through a variety of methods that could include chemoluminescence or electrochemoluminescence based approaches, single molecule measurements, liquid chromatography, or mass spectrometry, among others. Also, coding and noncoding RNA species (such as miRNAs, circRNAs, etc.) may also be evaluated.

The samples and any derived material will be destroyed ≤10 years after the end of the study.

10.9 Order of Assessments

The screening assessments can be performed in any order for the best evaluation of eligibility, at the discretion of the investigator.

Beginning at Visit 3 and onward, the assessments should be administered in the following order:

- PROs (PGI-S, COMPASS-S/SC, EQ-5D-5L)/Observer-reported outcome (OGI-S)
- Clinician-reported outcomes (UMSARS, CGI-S, SE-ADL)
- Safety assessments including ECG and safety labs
- Other assessments such as pre-dose PK assessments, blood biomarkers and CSF collection
- IMP administration. At visits with multiple PK assessments (Baseline, Visit 9 and Visit 15), PK blood sampling will take place after IMP administration as well

10.10 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 377 mL during the DBP, additionally, approximately 136 mL may be sampled for patients completing OLE, for patients undergoing the Withdrawal Visit 20 mL will be sampled. Up to 22 to 24 mL total of CSF will be collected from lumbar puncture procedures.

Additional blood samples may be required if the original blood samples are not viable or if re-testing is required.

The biobank blood samples and any derived material for potential future exploratory gene expression profiling or metabolic or proteomic biomarker analyses will be destroyed ≤10 years after the end of the study (see definition in volume of blood section 9.8).

The biobank blood samples and any derived material for potential future exploratory pharmacogenetic analyses will be destroyed ≤15 years after the end of the study (see definition in section 9.8).

To extend the retention period, the biobank blood samples and any derived material for potential future exploratory pharmacogenetic/gene expression analysis will be made anonymous by destroying the code key stored at specify location. When a blood sample or any derived material has been made anonymous, it cannot be traced back to the patient.

10.11 Treatment Compliance

IMP will be administered by a qualified healthcare professional. The exact doses and times of administration will be recorded in the eCRF.

11 Adverse Events

11.1 Definitions

11.1.1 Adverse Event Definitions[19]

Adverse event – is any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, ECG, C-SSRS), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

Worsening of concomitant illness and medical history
Medical conditions, which existed prior to the time of informed consent into the clinical study are part of the patient's medical history and are not considered an adverse event. Unchanged, chronic, non-worsening or sign/symptoms considered as part of the natural progression of the disease or pre-existing conditions from the time of informed consent are not adverse events and should not be reported as such. A clinically significant worsening of a pre-existing or chronic condition (for example, worsening of asthma) must be reported as an adverse event.

Worsening of MSA
Sign/symptoms/diagnosis related to known natural progression of MSA or re-emergence or worsening of MSA should not be reported as adverse events, except if fulling the seriousness criteria listed below.

Sign/symptoms/diagnosis (non-serious and serious adverse events) not considered part of the natural progression of MSA according to the investigator judgement should be reported as adverse events.

Fall
Falls fulfilling one or more seriousness criteria should be reported as a SAE. Falls that do not fulfil one or more seriousness criteria should not be reported as an adverse event. Clinically significant consequences (for example, cerebral trauma, fractures) of falls should be reported as a separate SAE.

An adverse event includes any changes in any safety assessment (including C-SSRS, out-of-range values from laboratory test results, MRI, vital signs and ECGs) which are clinically significant, that is, an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment, further investigations or more frequent follow-up due to the abnormality.

It is Lundbeck policy to collect and record all adverse events, including pre-treatment signs and symptoms, that is, those that start after the patient has signed the *Informed Consent Form* and prior to the first dose of IMP.

Serious adverse event – is any adverse event that:
- Results in death
- Is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the patient signed the *Informed Consent Form* and that did not change in intensity are not adverse events. Emergency room visits that do not result in admission to the hospital are not necessarily SAEs; however, they must be evaluated to determine whether they meet any of the SAE definitions (for example, life-threatening or other serious [medically important] event).

Non-serious adverse event – is any adverse event that does not meet the definition of an SAE.

If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

Suspected unexpected serious adverse reaction– is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure*[7]), and related to a medicinal product by either the investigator or Lundbeck.

Overdose – is a dose taken by a patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) must, at a minimum, be recorded as a non-serious adverse event.

11.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

The investigator must assess the *intensity* of the adverse event using the following definitions, and record it on the *Adverse Event Form*:

- *Mild* – the adverse event causes minimal discomfort and does not interfere in a significant manner with the patient's normal activities.
- *Moderate* – the adverse event is sufficiently uncomfortable to produce some impairment of the patient's normal activities.
- *Severe* – the adverse event is incapacitating, preventing the patient from participating in the patient's normal activities.

Assessment of Causal Relationship

The investigator must assess the *causal relationship* between the adverse event and the IMP using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Probable* – the adverse event has a strong temporal relationship to the IMP or recurs on re-challenge, and another aetiology is unlikely or significantly less likely.
- *Possible* – the adverse event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
- *Not related* – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent disorder or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

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

For pre-treatment adverse events, a causality assessment is not relevant.

Assessment of Outcome

The investigator must assess the *outcome* of the adverse event using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Recovered* – the patient has recovered completely, and no symptoms remain.
- *Recovering* – the patient's condition is improving, but symptoms still remain.
- *Recovered with sequelae* – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the patient's condition has not improved, and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death.*

11.1.3 Study-specific Adverse Event Definitions – Adverse Events Requiring Additional Data Collection

Adverse events (any sign or symptom) which are experienced by the patient during and/or after the infusion of the IMP and which are likely to be immunologically mediated should be considered a hypersensitivity reaction and additional data collection is required as adverse events requiring additional data collection. Anaphylaxis represents a subgroup of hypersensitivity reactions. If a systemic hypersensitivity reaction occurs, a tryptase blood sample will be drawn from the patient after the event, see below.

For key clinical features of hypersensitivity reactions including anaphylaxis and immune-complex related reactions, please refer to Appendix III.

For adverse events requiring additional data collection, a specific hypersensitivity form[20] must be completed in the eCRF in addition to the *Adverse Event Form* (see Appendix V for more details about the hypersensitivity form). For systemic hypersensitivity reactions adverse events requiring additional data collections (as defined in Appendix III), additional blood samples must be collected at the site and results recorded in the eCRF (*Hypersensitivity Form*):

- Serum total tryptase collected as per central laboratory procedures: optimally to be collected between 30 minutes to 2 hours after symptom onset. At least 24 hours after total resolution of sign and symptoms and in due time (expected 10 days of return of test results) prior to next IMP dosing the investigator must call the patient in for an unscheduled visit to collect a serum total tryptase sample to evaluate baseline level making sure to receive the results in time for the next IMP dosing. The investigator must assess the result (see below) prior to next IMP dosing.

A clinically significant increase of serum total tryptase at the time of systemic hypersensitivity reaction of >2 ng/mL+1.2 × patient's baseline serum total tryptase supports the diagnosis of anaphylaxis.[21] Systemic hypersensitivity reaction algorithm described in Appendix V.

11.1.4 Management of Reactions to Study Drug

There is no specific antidote to an infusion of Lu AF82422.

A medical emergency should be treated appropriately by the investigator using proper standard of care, according to their typical clinical practice and local guidelines for that emergency condition.

Should a medical condition arise that the investigator believes is related to the study drug, clinical judgement should be used to provide the appropriate response including the consideration of pausing or discontinuation of the IMP. Any events believed to be allergic reactions should be discussed with the medical monitor.

11.2 Pregnancy

Although not necessarily considered an adverse event, a pregnancy in a patient in the study must be recorded on an *Adverse Event Form*, as well as on a *Pregnancy Reporting Form* (paper), even if no adverse event associated with the pregnancy has occurred. Pregnancies must be reported to Lundbeck using the same expedited reporting timelines as those for SAEs.

An uncomplicated pregnancy should not be reported as an SAE; hospitalization for a normal birth should not be reported as an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion must be indicated on the *Serious Adverse Event Form*. Examples of pregnancies to be reported as SAEs (medically important) are spontaneous abortions, stillbirths, and malformations.

The investigator must follow-up on the *outcome* of the pregnancy and report it on a *Pregnancy Outcome Form* (paper). The follow-up must include information on the neonate at least up until the age of 1 month.

If the partner of a man participating in the study becomes pregnant, the pregnancy should be reported on the *Pregnancy Reporting Form* (paper) and the outcome of the pregnancy should be followed and reported (*Pregnancy Outcome Form*) if the partner agrees. The partner must sign a pregnant partner *Informed Consent Form* to allow the investigator to collect information to report to Lundbeck.

11.3 Recording Adverse Events

Adverse events (including pre-treatment adverse events after signing *Informed Consent Form*) must be recorded on an *Adverse Event Form*. In addition, if the adverse event fulfils the definition of an adverse event requiring additional data collection, a specific *Hypersensitivity Form* must be filled out (for further details on the content of the form, see Appendix IV). The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours or occurs on the day of IMP administration); intensity; causal

relationship to the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative aetiology must be recorded, if available. If the adverse event is an overdose, underdose, the nature of the overdose/underdose must be stated (for example, medication error, accidental overdose). Other medication errors for example, wrong technique of infusion, wrong infusion rate etc. should likewise be recorded. If the intensity changes during the course of the adverse event, this must be recorded on the *Adverse Event Intensity Log*.

If the adverse event is *serious*, this must be indicated on the *Adverse Event Form*. Furthermore, the investigator must fill out a *Serious Adverse Event Form* and report the SAE to Lundbeck immediately (within 24 hours) after becoming aware of it (see section 11.4).

If individual adverse events are later linked to a specific diagnosis, the diagnosis should be reported and linked to the previously reported adverse events.

11.4 Reporting Serious Adverse Events

The investigator must report SAEs to Lundbeck immediately (within 24 hours) after becoming aware of them by completing a *Serious Adverse Event Form* in the eCRF.

The initial *Serious Adverse Event Form* must contain as much information as possible and, if more information about the patient's condition becomes available, the *Serious Adverse Event Form* must be updated with the additional information.

If the investigator cannot report the SAE in eCRF (Rave®), then he or she must complete and sign the *Serious Adverse Event Fallback Form* and send it to:

Fax: +45 36 30 99 67
email: ICSRquery@lundbeck.com

If sent by email, the investigator must ensure that the *Serious Adverse Event Fallback Form* is sent password protected and that the password is sent in a separate email.

If the SAE, reported on the *Serious Adverse Event Fallback Form*, concerns an adverse event requiring additional data collection, the investigator must complete and sign the *Hypersensitivity Form* and send it together with the *Serious Adverse Event Fallback Form*.

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local requirements.

It is the investigator's responsibility to be familiar with local requirements regarding reporting of SAEs to the EC or IRB and to act accordingly.

11.5 Treatment and Follow-up of Adverse Events

Patients with adverse events must be treated in accordance with usual clinical practice at the discretion of the investigator.

The investigator must follow-up on non-SAEs until resolution or completion of a Safety Follow-up Visit, whichever comes first. At the Safety Follow-up Visit, information on new adverse events (non-serious and serious adverse events), if any, and stop dates for previously reported adverse events must be recorded.

The investigator must follow-up on all SAEs until the patient has recovered, stabilized, or recovered with sequelae, and report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial *Serious Adverse Event Form*.

SAEs that are spontaneously reported by a patient to the investigator after completion of the Safety Follow-up Visit must be handled in the same manner as SAEs that occur during the study. These SAEs will be recorded in the Lundbeck safety database.

Patients with a clinically significant out-of-range clinical safety laboratory test value at an EoT or any Withdrawal Visit must be followed in accordance with usual clinical practice. If the clinically significant out-of-range clinical safety laboratory test value has not normalized or stabilized or a diagnosis or a reasonable explanation has not been established by the Safety Follow-up Visit, the investigator must decide whether further follow-up visits are required (this may include an additional medical examination and/or additional blood sampling). If further follow-up visits are made, these must be documented in the patient's medical records and not in the eCRF.

Patients who withdraw due to an elevated AST or ALT value (see section 6.4) must be followed until the values normalize or stabilize or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, prothrombin time) should be considered. A gastroenterology or hepatology consultation should also be considered.

For patients who attend the DBP Safety Follow-up Visit before entering the OLE:

The investigator must continue to follow-up on non-SAEs until resolution or completion of the SFU-E Visit, whichever comes first. At the SFU-E Visit, information on new adverse events (non-serious and serious adverse events), if any, and stop dates for previously reported adverse events must be recorded.

11.6 Study Monitoring Committee(s)

11.6.1 Independent Data Monitoring Committee

The iDMC is an independent, external committee composed of members whose expertise covers relevant specialities. In the DBP, the iDMC will monitor SAEs on an on-going basis in addition to cumulative safety data including adverse events at pre-defined time points (every 3 months ±1 month) as well as adhoc. This is in order to protect the safety of the patients and to evaluate the safety risk. The iDMC will have access to unblinded data, and will provide recommendations on study continuation, modification or termination. The iDMC will be informed to what extent the data and analyses provided to them have been quality controlled. Members of the DMC will not be involved in other study-related tasks.

The iDMC procedures are described in the *DMC Charter*.

12 Data Handling and Record Keeping

12.1 Data Collection

12.1.1 Electronic Case Report Forms

eCRFs will be used to collect all the data related to the study, except the external data described in section 12.1.2.

This data collection tool is a validated electronic data capture (EDC) system that contains a system generated audit trail. Data required according to this protocol are recorded by web based EDC software system (Rave®). The investigator shall ensure that all data from participant visits are promptly entered into the eCRFs (ideally during the visit or as soon as possible <3 days thereafter), in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal designated CRO and external investigational site personnel seeking access to the eCRF are supported by Lundbeck Rave System Administration and Medidata Helpdesk. Access to the system will only be granted after appropriate and documented training.

As a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the participant's file.

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, independent ethics committee (IEC)/IRB review and regulatory inspection.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

12.1.1.1 Serious Adverse Event Fallback Forms

Serious Adverse Event Fallback Forms must be used when the eCRF cannot be accessed (see section 11.4).

12.1.2 External Data

All electronic data will be transferred using a secure method accepted by Lundbeck.

The following electronic data will be transferred by the vendor and kept in a secure designated storage area outside the eCRF:

- IMP quantification data (including CSF)

- Biomarker analysis data (including CSF)
- ECG data
- Clinical Safety Laboratory data
- PAMSys
- Biobanking data: RNA, Metabolomics/Proteomics, DNA (optional)
- FeetMe®
- MRI data
- ADAs
- Exit Interviews/Study Experience Interviews will be audio-recorded and then transcribed verbatim. As audio-recordings will not be retained, transcripts will be de-identified and considered source documents.

The following electronic data will be captured within the Medidata and MedAvante-Prophase (covering electronic COA [eCOA] for UMSARS) systems as a separate application.

- eDiary
- eCOA

The following electronic data will be captured in Medidata and processed by Mayo Clinic

- COMPASS-S and COMPASS-SC

12.2 Retention of Study Documents at the Site

12.2.1 eCRF Data

If a site closes before the study has been completed, the investigator will continue to have read-only access to the eCRF until the study has been completed. After the study has been completed, all user access to the eCRF will be revoked. Renewed access to the eCRF will be given if corrections or updates to the database are required.

At the end of the study, the site will be provided with all data related to the site (including eCRF data, queries, and the audit trail) using a secure electronic medium; the secure storage of these data at the site is the responsibility of the investigator. When confirmation of receipt of the data has been received from all sites, all user access to the eCRF will be revoked. If, for some reason, the data are not readable for the full retention period (25 years or in accordance with national requirements, whichever is longer), the investigator may request that the data be re-sent.

12.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF for at least 25 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer. Lundbeck will remind the investigator in writing of this obligation when the *Clinical Study Report Synopsis* is distributed to the site.

If off-site storage is used, a study-specific binder will remain at the site after the other study-specific documents have been shipped for off-site storage. This binder is considered part of the investigator TMF and must be kept in a secure place by the site for the required period of time. The binder must contain, at a minimum, the following documents: a copy of the *Investigator TMF Index*, a certified copy of the *Patient Identification Code List*, and a *Retrieval Form*.

When the required storage period has expired, the documents may be destroyed in accordance with regulations.

13 Monitoring Procedures

Prior to allowing patients to participate in the study, the investigator must sign a source data agreement that identifies the source documents (original documents, data, and records) at the site. The document will also list which data may be recorded directly on the eCRFs.

If the investigator does not have a patient's medical records, the investigator must attempt to obtain copies or a written summary of relevant medical records from the doctor who had treated the patient earlier and include the pertinent documentation in the patient's medical records at the site. The investigator must obtain medical records documenting the patient's lifetime episodes and general medical history for the 3 months prior to the study.

During the study, there will be both blinded and unblinded monitoring visits conducted by CRAs to ensure that the protocol is being adhered to and that all issues are being recorded, and to perform source data verification. The blinded monitoring visit will focus on the procedures involving direct patient care. The unblinded monitoring visit will focus on IMP accountability and maintaining the blind. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the site's recruitment rate, and the compliance of the site to the protocol and *Good Clinical Practice*. In addition, the CRA will be available for discussions by telephone.

Source data verification requires that the CRA be given direct access to all the source documents. Direct access includes permission to examine and verify any records that are important for the evaluation of the study.

It must be possible to verify all other data in the eCRFs against source documents in the patient's medical records, or in the location stated in the source data agreement.

COVID-19 mitigation strategy for CRAs will be captured in a living, constantly updated document "COVID-19 Mitigation Plan" describing the respective contingency measures.

14 Audits and Inspections

Authorized personnel from Medical, Regulatory and Clinical Quality Assurance, H. Lundbeck A/S, and quality assurance personnel from business partners may audit the study at any time to assess compliance with the protocol and the principles of *GMP* and all other relevant regulations.

The investigator must be aware that representatives from regulatory authorities may also wish to inspect source data, such as medical records. The investigator must notify Lundbeck and designated CRO, without delay, of an announced inspection by a regulatory authority.

During audits and inspections, the investigator must permit direct access to all the source documents, including medical records and other documents pertinent to the study.

During audits and inspections, the auditors and inspectors may request relevant parts of medical records. No personal identification apart from the screening or randomization numbers will appear on these copies.

Patient data will not be disclosed to unauthorized third parties, and patient confidentiality will be respected at all times.

15 Protocol Compliance

Lundbeck has a “no-waiver” policy, which means that permission will not be given to deviate from the protocol.

If a deviation occurs, the investigator must inform the CRA and they must review, discuss, and document the implications of the deviation.

16 Study Termination

Lundbeck or a pertinent regulatory authority may terminate the study or part of the study at any time. The reasons for such action may include, but are not limited to:

- Safety concerns
- Proven lack of efficacy of the IMP in other studies

If the study is terminated or suspended, the investigator must promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or sponsor must promptly inform the EC or IRB and provide a detailed written explanation. The pertinent regulatory authorities must be informed in accordance with national regulations.

If the risk/benefit evaluation changes after the study is terminated, the new evaluation must be provided to the EC or IRB if it will have an impact on the planned follow-up of the patients

who participated in the study. If so, the actions needed to protect the patients must be described.

17 Statistical Methodology

17.1 Study Primary Estimand

The following primary estimand is defined for this study:

CCI
CCI
CCI
CCI
CCI
CCI
CCI
CCI

Handling of IE's

- CCI

A key secondary study estimand will be defined CCI
CCI

For evaluating the appropriateness of this strategy, a number of sensitivity analyses will be performed using different imputation strategies. For additional information see section 17.9.3: Sensitivity Analyses of the Primary Endpoint(s) (also covering sensitivity analysis for the key secondary endpoint) and the study SAP.

17.2 Responsibilities

The responsibility for performing the below described statistical analysis will be at Lundbeck. All analyses will be based on data received from ICON.

17.3 Analysis Sets

The patients and data will be classified into the analysis sets according to these definitions at a *Classification Meeting* held after the study database has been released, but before the blind has been broken (except for the PK subset which will be classified after unblinding).

- *all-patients-randomized set* (APRS) – all randomized patients
- *all-patients-treated set* (APTS) – all patients in the APRS who received at least one dose of double-blind IMP
- *all-patients-treated-follow-up set* (APTS-FU) – all patients in the APTS who complete the DBP and who has data collected up to and at the Safety Follow-up DBP Visit
- *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 Part I and Part II, prior to, or at withdrawal from treatment in the DBP
- *PK subset* (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
- *exit interview subset* (EIS) – all patients in the FAS having a complete Exit interview with the patient and/or the caregiver
- *study experience interview subset* (SEIS) – 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

The efficacy analyses will be based on the FAS and the OLES, and the safety analyses will be based on the APTS, APTS-FU, and the OLES unless otherwise specified. Listings will be based on the APRS.

17.4 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, 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.

17.5 Patient Disposition

Patient disposition will be summarized by period and treatment group and include the number of patients in the APTS who completed or withdrew from treatment, as well as the number of patients in each analysis set (APRS, APTS, FAS, PKS, SBS, EIS, SEIS, and OLES).

The number of patients who completed or withdrew from the study will also be summarized.

The number of patients who withdrew from treatment will be summarized by period and treatment group and primary reason for withdrawal as well as by treatment group and all reasons for withdrawal. A Kaplan-Meier plot will be presented for time-to-withdrawal for all reasons per treatment group, if appropriate.

17.6 Demographics and Baseline Characteristics

Demographics (sex, age, race, and region), baseline characteristics (weight, body mass index [BMI], and possible or probable MSA-P or MSA-C), baseline efficacy variables, and other disease characteristics will be summarized by treatment group for the DBP.

17.7 Recent and Concomitant Medication

Recent and concomitant medication will be summarized by anatomical therapeutic chemical (ATC) code and generic drug name by period and treatment group.

17.8 Exposure and Compliance

Exposure and compliance will be calculated per patient and summarized by period and treatment group.

17.9 Efficacy Analyses

17.9.1 General Efficacy Analysis Methodology

Unless otherwise specified, all the efficacy analyses for the DBP will be based on the FAS. All endpoints will be presented with descriptive statistics and the one-sided 95% confidence intervals for both absolute values and change from baseline. Histograms will be explored and presented for the UMSARS scores observed cases; otherwise only in case of compromising findings for the secondary endpoints.

Since the primary, key secondary and selected secondary analyses for the UMSARS scores will be performed in a Bayesian framework, the success threshold for the Bayesian posterior probability of superiority relative to placebo will be calibrated through simulations to correspond to a significance level of 5% evaluated one-sided. For the frequentist analyses, the significance level will be 5%, which will be applied one-sided.

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 for these analyses. Further details in the section 17.9.4, Testing Strategy.

Efficacy analyses for the OLE will be exploratory based on the OLES. All patients in the OLE will receive active treatment. However, patients receiving placebo in the DBP and hence switching treatment will be defined and handled as a separate group.

17.9.2 Primary Analysis of the Primary Endpoint(s)

The primary efficacy analysis of UMSARS TS following up to 72 weeks of treatment in the DBP will be based on a Bayesian repeated measures model of the change from baseline through up to 72 weeks. Thus, also defined as the estimator used for the primary estimand. The repeated measures model will be based on observed cases only (that is, no imputation) and incorporates the following features:

- Fixed effects for change in UMSARS TS progression per visit: 12, 24, 36, 48, 60, and 72 weeks
- Participant-level random effects for the rate of UMSARS progression across visits
- Fixed multiplicative treatment effect, θ, for increase or decrease in the overall rate of UMSARS progression of Lu AF82422 relative to placebo common across all visits. In particular, if θ<1, the active treatment slows the rate of progression of UMSARS relative to placebo. If θ>1, the active treatment increases the rate of progression of UMSARS relative to placebo. If θ = 1, the rate of progression of UMSARS 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 for CCI and region (US and Japan) common across all visits
- Prior distribution for model parameters selected in a conservative and non-informative manner using relatively large outcome spaces

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 = 10,000 draws from the joint posterior distribution for all model parameters. In particular, summaries of the Bayesian posterior distribution for the treatment effect compared to placebo, θ, will be provided including the mean, median and 95% credible intervals; the probability that Lu AF82422 is superior to placebo, Pr ($\theta < 1$), which constitutes the primary analysis of the study; Additionally, the probability the treatment slows the rate of progression by at least 10%, Pr ($\theta < .9$); and the probability the treatment slows the rate of progression by at least 20%, Pr ($\theta < .8$), will be provided.

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

17.9.3 Sensitivity Analyses of the Primary Endpoint(s)

Sensitivity analyses to the primary analysis will be performed evaluating, in particular, the model assumptions (effect proportionality, etc.), performance (sensitivity to priors, potential bias, etc.) and the impact of missing data; with special focus of events of death and drop-outs with no follow-up data available. For these events, different imputation strategies will be applied and evaluated in a parametric setting.

In addition, a non-parametric worst-rank analysis will be performed to account for informatively missing data by ranking patients based jointly on their last available UMSARS score and mortality.

Further details on sensitivity analyses are in the study SAP.

17.9.4 Testing Strategy

To protect the type I error for the primary analysis, that is, analysis of UMSARS TS and the key secondary analysis, that is, 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).

The applied success thresholds for the posterior probabilities will be identified through simulations and will be specified in the study SAP.

17.9.5 Analysis of the Key Secondary Endpoint

For the key secondary endpoint, that is, the changes in mUMSARS from baseline up to EoT, 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 17.9.3.

17.9.6 Analysis of the Secondary Endpoint(s)

For secondary endpoints in the DBP the following methodology will be applied:

- For the secondary endpoints UMSARS Part I and UMSARS Part II up to EoT, a Bayesian repeated measures model will be applied similar to the primary analysis.

- For remaining continuous secondary endpoints (for example, clinical scales/assessments and MRI volumetric parameters), a Mixed Model for Repeated Measurements (MMRM) will be applied to the changes from baseline up to Week 72. If required, a log transformation will be applied for normalization. The model will contain the following effects: baseline score, treatment, visit, baseline blood NfL, Region, treatment*visit and baseline score*visit as fixed effects and subject as random effect. Treatment estimates will be derived for each subsequent visit. The primary comparison will be at Week 48, whereas Week 72 will be exploratory. Initially, an unstructured covariance matrix will be fitted. In case of issues converging, a Compound Symmetry structure will be used.
- All categorical secondary endpoints will be analyzed applying a logistic regression. Treatment effect evaluated at Week 48 will be primary.
- Number of falls per individual per fall diary period, according to the patient fall diary, will be analyzed applying a negative binomial regression model.
- Additional time-to-event secondary and exploratory endpoints following 48 weeks and 72 weeks of treatment will be analyzed applying a Cox proportional-hazards model. Week 48 will be primary.
- Lu AF82422 plasma concentrations, CSF concentrations, and the CSF/plasma concentration ratios during treatment for all patients will be presented descriptively. The data will be included in a separately reported population PK analysis.
- Absolute values and changes from baseline up to Week 48 and Week 72 in blood biomarkers and Week 48 in CSF biomarkers will be analyzed descriptively. For selected parameters, a MMRM will be applied for the changes from baseline to EoT. If required, a log transformation will be applied for normalization.
- TE of Lu AF82422 to α-synuclein in CSF will be presented descriptively as “free” synuclein, “total” α-synuclein and ratio of “free” to “total” α-synuclein.
- Gait and balance parameters derived from the sensor-based FeetMe® device will primarily be analyzed descriptively for the SBS. If appropriate, a MMRM model, like the one described above for continuous secondary and exploratory endpoints, will be applied. Correlation to the key progression markers, that is the UMSARS scores and MRI parameters, will be explored graphically.
- The potential influence of covariates (in addition to CCI and region) will be investigated using a frequentist repeated measures analysis with fixed effects. Among the covariates to be investigated are age, gender, country, race, time-since-diagnosis, dose of Parkinson’s disease medication (expressed as levodopa equivalent daily dose [LEDD]), baseline MRI signal, and baseline plasma/CSF α-synuclein and MSA sub-type.
- Use of concomitant medication and changes in medication during the course of the study will be presented and compared descriptively across treatment arms.

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

- Relationships between selected continuous endpoints, that is, UMSARS total and sub-domains, COMPASS-S/SC, CGI-S, PGI-S, OGI-S, SE-ADL, gait parameters and EQ-5D-5L will be explored, at least through correlation analysis on absolute values and change from baseline. In addition, correlation between UMSARS, MRI, blood/CSF NfL, α-synuclein and other potential biomarkers will likewise be explored.

- The minimal clinically important difference within-patient (MCID) on each scale will be estimated for example, with an anchor-based method estimating MCID based on the CGI-S scale accompanied by density- and cumulative distribution function curves of change in each scale from baseline to Week 72 with one curve per CGI-S score (at Week 72). Further details on the work identifying the MCID will be described in a specific separate *Psychometric SAP*.

17.9.7 Analysis of the Exploratory Endpoint(s)

For exploratory endpoints in the DBP the following methodology will be applied:

- For continuous exploratory endpoints, a MMRM will be applied for observed data, combined with imputation with worst-rank following events of death, if applicable, and 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, baseline blood NfL, region, treatment*visit and baseline score*visit as fixed effects and subject as random effect. The primary comparison will be at Week 48 and Week 72, respectively. Initially, an unstructured covariance matrix will be fitted. In case of issues converging, a Compound Symmetry structure will be used.
- Categorical exploratory endpoints up to EoTDBP will be analyzed applying a logistic regression.
- Time-to-event exploratory endpoints up to EoTDBP will be analyzed applying a Cox proportional-hazards model.
- Number of falls per individual according to the sensor-based PAMSys device will be analyzed applying a negative binomial regression model, if applicable, including data from the pre-defined periods only.
- The analysis of semi-structured, qualitative Exit interviews will be pre-specified in a specific Qualitative Analysis Plan (QAP). Whenever a combined quantitative and qualitative approach is considered to analyze these interviews, a Mixed Methods Qualitative Analysis Plan (MM-QAP) will be developed.

Analysis of OLE effect data:

- Analysis of exploratory efficacy data collected in the OLE will be based on the OLES where the original placebo patients will be handled as a separate group.
- All continuous endpoints in the OLE will primarily be analyzed descriptively presenting both actual values and changes from baseline, where changes will be calculated using both the baseline from the DBP and the baseline from the OLE, respectively. In addition, an exploratory MMRM as described above will be applied to the changes from the DBP baseline visit. No formal testing will be applied.

17.9.8 Analysis of Subgroups

Subgroup Analyses of the Primary Endpoint will be performed using the Bayesian repeated measures primary analysis model by adding selected subgroups as multiplicative fixed covariate effects. For this purpose, the model will be excluding effects of CCI and region, respectively. Among the subgroups to be investigated are:

- age (categorized as <50 years; 50 to 60 years; >60 years)
- MSA subgroup and diagnosis certainty (possible/probable MSA-P/-C)
- gender (female/male)
- country (with small countries pooled)
- race
- time-since-diagnosis (as yearly intervals)
- use of concomitant and PD medication (expressed; both categorized appropriately prior to database release) as LEDD
- baseline MRI atrophy and diffusivity (grouped using 25th and 50th percentiles)
- baseline plasma/CSF α-synuclein and CSF NfL (grouped using 25th and 50th percentiles)
- baseline disease severity according to CGI-S and SE-ADL (grouped using 25th and 50th percentiles) and UMSARS part IV
- occurrence of ADAs, that is, ADA positive vs. ADA negative patients

17.10 Safety Analyses

17.10.1 Analysis of Adverse Events

Adverse events will be classified according to the time of onset of the adverse event:

- *pre-treatment adverse event* – an adverse event that starts on or after the date the patient signed the *Informed Consent Form* and prior to the date of first dose of IMP
- *treatment-emergent adverse event* – an adverse event that starts or increases in intensity during or after administration of first dose of IMP

Adverse events, sorted by system organ class and preferred term, will be summarized by period and treatment group.

Data on adverse events related to systemic hypersensitivity reaction collected via the dedicated *Hypersensitivity Form* will likewise be summarized by period and treatment group.

Allocation of TEAEs to Study Periods

TEAEs will be assigned to periods according to the following:

- *Adverse events in the DBP* – all TEAEs with date of onset or worsening of intensity/seriousness after first dose of IMP in the DBP and until final visit at EoTDBP (assigned APHASE = DOUBLE-BLIND)
- *Adverse events in the Safety Follow-up Period in the DBP* – TEAEs with date of onset or worsening of intensity/seriousness occurring in the Safety Follow-up Period following the DBP (assigned APHASE = SAFETY)
- *Adverse events in the OLE* – TEAEs with date of onset or worsening of intensity/seriousness after first dose of IMP in the OLE (assigned APHASE = TEP)

- *Adverse events in the Safety Follow-up Period in OLE* – TEAEs with date of onset or worsening of intensity/seriousness occurring in the Safety Follow-up Period (SFU-E) following the OLE treatment period (assigned APHASE = SAFETY_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 on-going at the end of the EoTDBP Visit, which worsens after the EoTDBP Visit, will be reported both for the DBP and the Safety Follow-up Period/OLE whichever follows the DBP.

17.10.2 Analysis of Other Safety Endpoints

The clinical safety laboratory test values, vital signs, ECG parameter values, ADA, safety MRI findings and C-SSCS will be summarized by period and treatment group. Potentially clinically significant (PCS) values will be flagged and summarized.

17.11 Interim Analyses

No interim analyses will be performed for this study.

17.12 Sample Size and Power

CCI
CCI
CCI
CCI

CCI

CCI

CCI

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 one-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 (that is, 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.

17.13 Statistical Analysis Plan

A *Study Statistical Analysis Plan,* a *Psychometric Statistical Analysis Plan* and a *Qualitative Analysis Plan* describing the detailed handling of data issues and the planned analyses in more detail will be prepared by Lundbeck or Lundbeck's designees before database release.

18 Clinical Study Report and Publications

18.1 Data Ownership

The data collected in this study are the property of Lundbeck.

18.2 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared.

18.3 Summary of Clinical Study Results

Upon completion of the study and when the study results are available, the patient has the right to be informed by the investigator about the overall study results.

18.4 Publications

The results of this study will be submitted for publication.

Lundbeck will submit results information to ClinicalTrials.gov.

The primary publication based on this study must be published before any secondary publications. Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).[22]

19 Indemnity and Insurance

In the event of study-related injuries or deaths, insurance for the patients and indemnity of the investigators and those of their employees, servants, or agents whose participation in this study has been documented are provided. Insurance and liability will be in accordance with applicable laws and *GMP*.

20 Finance

20.1 Site Agreements

The financial agreements with each site are addressed in one or more documents. Both parties must sign the agreements before each site is initiated.

20.2 Financial Disclosure

All the investigators, including sub-investigators, and raters participating in the study must complete a *Financial Disclosure Form*.

20.3 Equipment

Equipment owned or rented by Lundbeck that has been provided to the sites for use during the study must be returned at the end of the study.

Reference

1. Fanciulli A, Wenning GK. Multiple-system atrophy. N Engl J Med. 2015; 372(3): 249-263.
2. Petrovic IN, Ling H, Asi Y, et al. Multiple system atrophy-parkinsonism with slow progression and prolonged survival: a diagnostic catch. Mov Disord. 2012;27(9):1186-1190.
3. Krismer F, Wenning GK. Multiple system atrophy: insights into a rare and debilitating movement disorder. Nat Rev Neurol. 2017;13(4):232-243.
4. Sakushima K, Nishimoto N, Nojima M, et al. Epidemiology of Multiple System Atrophy in Hokkaido, the Northernmost Island of Japan. Cerebellum. 2015;14(6):682-687.
5. Singer W, Low PA. Optimizing Clinical Trial Outline for multiple system atrophy: lessons from the rifampicin study. Clin Auton Res. 2015;25(1):47-52.
6. Colosimo, C., Tiple, D. & Wenning, G. Management of multiple system atrophy: state of the art. J Neural Transm 112, 1695–1704 (2005).
7. Investigator's Brochure, Lu AF82422, current version.
8. World Medical Association (WMA). Declaration of Helsinki: Ethical principles for medical research involving human subjects. [Internet] wma.net/en/30publications/10policies/b3/index.html.
9. ICH. ICH Harmonised Guideline E6(R2): Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice. November 2016.
10. Wenning GK, Tison F, Seppi K, et al. Multiple System Atrophy Study Group. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord. 2004;19(12):1391-402.
11. Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, eds. Third synopsium on Parkinson's disease. Edinburgh: Livingston, 1969:152-157.
12. Collection of Race and Ethnicity Data in Clinical Trials. Guidance for Industry and Food and Drug Administration Staff. FDA 26 Oct 2016.
13. ICH guideline E17 on general principles for planning and design of multi-regional clinical trials. Reference number EMA/CHMP/ICH/453276/2016, published 18 Dec 2017.
14. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H. Second consensus statement on the diagnosis of multiple system atrophy. Neurology. 2008 Aug 26;71(9):670-6.
15. Lipp A, Sandroni P, Ahlskog E, et al. Prospective Differentiation of Multiple System Atrophy from Parkinson Disease, With and Without Autonomic Failure.Arch Neurol 2009;66(6):742-750.
16. Suarez GA, Opfer-Gehrking TL, Offord KP, et al. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. Neurology. 1999 Feb;52(3):523-8.
17. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research. 2011;20:1727–1736.

18. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266–1277.

19. ICH. ICH Harmonised Tripartite Guideline E2A: Clinical safety data management: definitions and standards for expedited reporting. October 1994.

20. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler H J, Schlößer HA, Schlaak M, & von Bergwelt-Baildon MS (2018). Cytokine release syndrome. Journal for immunotherapy of cancer, 6(1), 56.

21. Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, Laguna JJ, Chiriac AM, Terreehorst I, Voltolini S, Scherer K. An EAACI position paper on the investigation of perioper-ative immediate hypersensitivity reactions. Allergy. 2019 Oct;74(10):1872-84.

22. International Committee of Medical Journal Editors (ICMJE). Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. [Internet] ic-mje.org/ic-mje-recommendations.pdf. December 2017.

Appendix I
Clinical Study Protocol
Authentication and Authorization

Clinical Study Protocol
Authentication and Authorization

Study 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
Study No.:	18331A
Edition No.:	6.0
Date of edition:	29 May 2024

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

Authentication

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Global Trial Manager:	PPD
Global Trial Lead:	
Head of Biostatistics:	
Head of Medical Safety:	

Authorization

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Therapeutic Area Lead:	Bjørn Aaris Grønning, Vice President, Clinical Development

Appendix II
Recent and Concomitant Medication Disallowed or Allowed with Restrictions

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

In the table below, recent and concomitant medications that are disallowed or allowed with restrictions with respect to their use prior to or during the study are listed.

Drug Class	Details
Disallowed:	
Any investigational products	Disallowed within 30 days before the Screening Visit or 5 half-lives – whichever is longer, and throughout the whole study
Inhibitor of α-synuclein aggregation	Treatment targeting α-synuclein and/or MSA disease progression within the last 12 months and throughout the whole study
Monoclonal antibodies	anti-α-synuclein monoclonal antibody within the last 12 months and throughout the whole study
Vaccines	past or current treatment with an active vaccine targeting α-synuclein and throughout the whole study
Allowed with restriction:	Drugs acting against parkinsonism or autonomic dysfunction
Anticholinergic agents	All, stable dose for at least 8 weeks prior to randomization
Anticholinesterases	All, stable dose for at least 8 weeks prior to randomization
Cardiac stimulants	Adrenergic and dopaminergic agents, stable dose for at least 8 weeks prior to randomization
Corticosteroids for systemic use	Fludrocortisone; stable dose for at least 8 weeks prior to randomization
Dopaminergic agents	All, stable dose for at least 8 weeks prior to randomization
Drugs for urinary frequency and incontinence	All, stable dose for at least 8 weeks prior to randomization
Hypothalamic hormones	Octreotide; stable dose for at least 8 weeks prior to randomization
Posterior pituitary lobe hormones	Vasopressin and analogues; stable dose for at least 8 weeks prior to randomization
If medically necessary, initiation of or change of dose of concomitant medication allowed with restriction is allowed per investigator discretion.	

Appendix III
Guidance for Key Clinical Features of Hypersensitivity Related Reactions

Guidance for Key Clinical Features of Hypersensitivity Related Reactions

Definition of Hypersensitivity reactions (study-specific adverse events requiring additional data collection)

- Type I hypersensitivity reaction: Anaphylaxis

Anaphylaxis is a serious, acute allergic reaction and involves specific immunoglobulin E (IgE) antibodies. The definition relies on clinical accepted diagnostic criteria.

National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria for Anaphylaxis:

Anaphylaxis is highly likely when any 1 of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST 1 OF THE FOLLOWING:

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Type II hypersensitivity reaction: Cytokine Release Syndrome (CRS)

CRS, also called anaphylactoid reactions are not IgE but cytokine mediated reactions. CRS is a symptom complex caused by the rapid release of pro-inflammatory cytokines from target immune cells and involves Fc-mediated functions of the drug product. *(Ref. FDA Guidance for industry: Immunogenicity Assessment for Therapeutic Protein Products - August 2014)*

Clinical signs can range from mild flu-like symptoms to severe life-threatening symptoms[20]. Mild symptoms of CRS include fever, fatigue, headache, rash, arthralgia, and myalgia. More severe cases are characterized by hypotension as well as high fever and can progress to an uncontrolled systemic inflammatory response with vasopressor-requiring circulatory shock, vascular leakage, disseminated intravascular coagulation, and multi-organ system failure. Respiratory symptoms are common in patients with CRS.

Mild cases may display cough and tachypnoea but can progress to acute respiratory distress syndrome (ARDS). In addition, laboratory abnormalities that are common in patients with CRS include cytopenias, elevated creatinine and liver enzymes, deranged coagulation parameters, and a high sensitivity C-reactive protein.

Type III hypersensitivity reaction: Immune-complex related reactions

Immune-complex related reaction is a delayed hypersensitivity ("Serum sickness") and secondary to immune-complex formation and complement activation.

Clinical signs may include delayed onset of fever, rash, arthralgia, myalgia, haematuria, proteinuria, serositis, CNS complications and hemolytic anaemia. *(Ref. FDA Guidance for industry: Immunogenicity Assessment for Therapeutic Protein Products -August 2014)*

Appendix IV
Hypersensitivity Form

Hypersensitivity Form

Study 18331A HYPERSENSITIVITY FORM

Date of the report:	Corresponding AE form number:
Name of investigator:	Site number:
Patient study randomisation number:	

For the current reported event:

Did the patient exhibit any of the following symptoms (tick as many as appropriate)?

Dermatologic/mucosal
- ▫ generalised erythema
- ▫ generalized urticaria (hives)
- ▫ angioedema specify site: .....
- ▫ generalized pruritus with skin rash
- ▫ generalized pruritus without skin rash
- ▫ generalised prickle sensation
- ▫ localized injection site urticaria
- ▫ itchy eyes with or without chemosis

Cardiovascular

▫ acute hypotension or worsening of pre-existing hypotension related to the immune reaction.
Please specify below BP measurements:

Systolic.....

Diastolic.....

▫ clinical diagnosis of uncompensated shock indicated by the combination of at least 3 of the following:
- tachycardia
- capillary refill time >3s
- reduced central pulse volume
- decreased level of consciousness or loss of consciousness

▫ clinical diagnosis of reduced peripheral circulation as indicated by the combination of at least 2 of the following:
- tachycardia
- capillary refill time >3s without hypotension
- decreased level of consciousness

Respiratory
- ▫ bilateral wheeze
- ▫ stridor related to the immune reaction
- ▫ upper airway swelling (lip, tongue, throat, uvula, or larynx)
- ▫ respiratory distress, 2 or more of the following:

tachypnoea
- increased use of accessory respiratory muscles
- recession
- cyanosis
- grunting

- ▫ persistent dry cough
- ▫ hoarse voice
- ▫ difficulty breathing without wheeze or stridor (related to the immune reaction)
- ▫ sensation of throat closure
- ▫ sneezing, rhinorrhoea

Gastrointestinal
- ▫ diarrhoea
- ▫ abdominal pain
- ▫ nausea
- ▫ vomiting

<table>
<tr><td colspan="2">Other symptoms, please specify:</td></tr>
<tr><td colspan="2">FOR SYSTEMIC HYPERSENSITIVITY REACTIONS</td></tr>
<tr><td colspan="2">□ Serum total tryptase at the time of the event
If yes, please provide:

Date of sample:

Hour of sample:

Value: --, --

Unit:

□ Not available</td></tr>
<tr><td>If multiple serum total tryptase are taken

□ serum total tryptase
If yes, please provide:

Date of sample:

Hour of sample:

Value: --, --

Unit:

□ Not available</td><td>

□ Serum total tryptase
If yes, please provide:

Date of sample:

Hour of sample:

Value: --, --

Unit:

□ Not available</td></tr>
<tr><td colspan="2">□ Baseline serum total tryptase:

If yes, please provide:

Date of sample:

Hour of sample:

Value: --, --

Unit:

□ Not available</td></tr>
</table>

Clinically relevant increase tryptase at time of reaction is defined as >2+1.2 x baseline serum total tryptase and support the diagnosis of anaphylaxis (ref. *An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions, Lene Heise Garvey and al., Allergy. 2019;1-13)*

□ Clinically relevant increase of tryptase (>2+1.2 x baseline serum total tryptase)

□ No clinically relevant increase of tryptase

How soon after the last infusion of IMP did the patient experience the first signs/symptoms (minutes/hours/days)?

_____

_____

Does the patient have any history of allergy or intolerances? Or has the patient experienced itching or cough after the use of a specific type of drug or ingestion of food?

□ yes □ no

If yes, please provide information

_____

_____

Are there other factors that may have contributed to the allergic reaction?

□ yes □ no

If yes, please describe

_____

_____

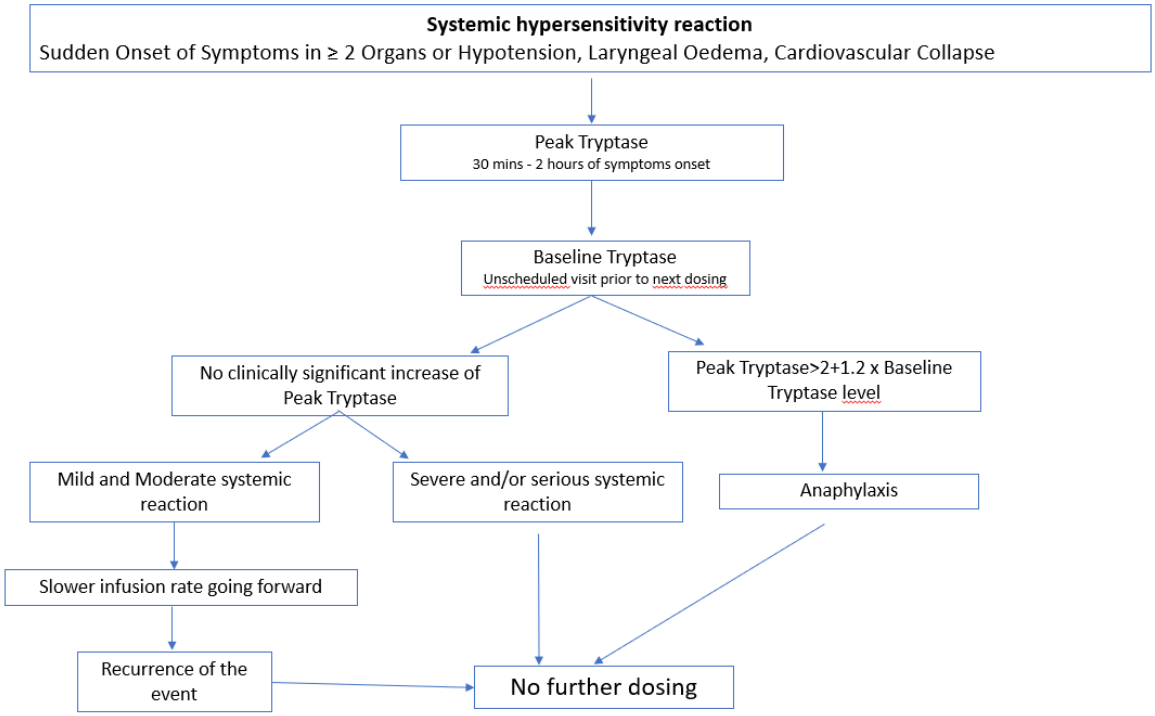
Please provide any further information that you believe may be relevant. If yes, please specify:

_____

_____

Your help in providing additional information regarding this case is appreciated.

Systemic Hypersensitivity Reaction Algorithm



Appendix V
Gilman Criteria

Gilman Criteria

Displayed below are the Gilman criteria[14]:

Probable MSA:

Criteria for the diagnosis of probable MSA
A sporadic, progressive, adult (>30 y)– onset disease characterized by
• Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic *and*
• Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

MSA multiple system atrophy.

Possible MSA:

Criteria for possible MSA
A sporadic, progressive, adult (>30 y)– onset disease characterized by
• Parkinsonism (bradykinesia with rigidity, tremor, or postural instability) *or*
• A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction) *and*
• At least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA) *and*
• At least one of the additional features shown in table 3

MSA multiple system atrophy.

Additional Features of Possible MSA:

Additional features of possible MSA
Possible MSA-P or MSA-C
• Babinski sign with hyperreflexia
• Stridor
Possible MSA-P
• Rapidly progressive parkinsonism
• Poor response to levodopa
• Postural instability within3y of motor onset
• Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction
• Dysphagia within5y of motor onset
• Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum
• Hypometabolism on fluorodeoxyglucose (FDG) -positron emission tomography (PET) in putamen, brainstem, or cerebellum
Possible MSA-C
• Parkinsonism (bradykinesia and rigidity)
• Atrophy on MRI of putamen, middle cerebellar peduncle, or pons
• Hypometabolism on FDG-PET in putamen
• Presynaptic nigrostriatal dopaminergic denervation on Single Photon Emission Computed Tomography or PET

MSA multiple system atrophy; MSA-P MSA with predominant parkinsonism; MSA-C MSA with predominant cerebellar ataxia; FDG [^{18}F]fluorodeoxyglucose.

Features Supporting (Red Flags) and not supporting a Diagnosis of MSA:

Features supporting (red flags) and not supporting a diagnosis of MSA

Supporting features	Nonsupporting features
• Orofacial dystonia	• Classic pill-rolling rest tremor
• Disproportionate antecollis	• Clinically significant neuropathy
• Camptocormia (severe anterior flexion of the spine) and/or Pisa syndrome (severe lateral flexion of the spine)	• Hallucinations not induced by drugs
• Contractures of hands or feet	• Onset after age 75 y
• Inspiratory sighs	• Family history of ataxia or parkinsonism
• Severe dysphonia	• Dementia (on DSM-IV)
• Severe dysarthria	• White matter lesions suggesting multiple sclerosis
• New or increased snoring	
• Cold hands and feet	
• Pathologic laughter or crying	
• Jerky, myoclonic postural/action tremor	

MSA multiple system atrophy; DSM-IV *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.