Appendix I.9

Statistical Analysis Plan (SAP)

Electronic Signature Page

Full Title
An open-label extension study to evaluate the long-term safety and tolerability of Lu AE58054 as adjunctive treatment to donepezil in patients with mild-moderate Alzheimer's disease

Short Title
14861B - Statistical Analysis Plan

Study Number 14861B

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Statistical Analysis Plan

An open-label extension study to evaluate the long-term safety and tolerability of Lu AE58054 as adjunctive treatment to donepezil in patients with mild-moderate Alzheimer's disease

Idalopirdine (Lu AE58054)

Study No.:	14861B
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SAP date:	10 July 2017

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List of Panels

List of Abbreviations and Definitions of Terms

γGT	γ-glutamyl transferase
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale, cognitive subscale
ADCS-ADL_{23}	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
FDA	United States Food and Drug Administration
IMP	investigational medicinal product
INR	international normalised ratio of prothrombin time
MMRM	mixed model for repeated measurements
MMSE	Mini Mental State Examination
NPI	Neuropsychiatric Inventory
PBO	placebo
PCS	potentially clinically significant
PR	specific ECG interval describing atrioventricular conduction
QP	qualified person
QRS	specific ECG interval describing ventricular depolarisation
QTcF	heart-rate corrected QT interval using Fridericia's correction formula
REML	restricted maximum likelihood
RUD Lite	Resource Utilisation in Dementia Lite
SADs	Lundbeck Standard Analysis Datasets
SAE	serious adverse event
SDTM	Standard Data Tabulation Model

SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 Objectives

1.1 Primary Objective

Open-label treatment period:

To evaluate the long term safety and tolerability of idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate AD.

Open-label treatment period with memantine (sub-study):

To evaluate the safety and tolerability of concomitant treatment with idalopirdine, memantine and donepezil in patients with mild-moderate AD.

1.2 Secondary Objective

Open-label treatment period:

To evaluate the long-term disease development during treatment with idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate AD.

Open-label treatment period with memantine (sub-study):

To evaluate the disease development during concomitant treatment with idalopirdine, memantine and donepezil in patients with mild-moderate AD.

1.3 Other Objectives

Open-label treatment period with memantine (sub-study):

To explore population pharmacokinetics.

2 Study Design

This is an interventional, multi-national, multi-site, open-label extension study in patients with mild to moderate AD who completed the 24-week "lead-in" double-blind, placebo controlled clinical studies 14861A and 14862A (from now on these studies will be referred to as “lead-in study” in the document). Randomized, blinded treatment in lead-in study will remain blinded to sites, CRAs, patients, and investigators until patients have completed the extension study (the sponsor will generally be un-blinded after unblinding of 14861A and 14862A occurs).

Patients completing the open-label treatment period and who will not continue into the 24-week open-label memantine sub-study (described below) will enter a 4-week safety follow-up period. Thus the total study duration of the open-label treatment period per patient from Baseline II (Visit 1 of the open-label treatment period and Visit 7 of the lead-in study) to the end of the follow-up will be approximately 32 weeks.

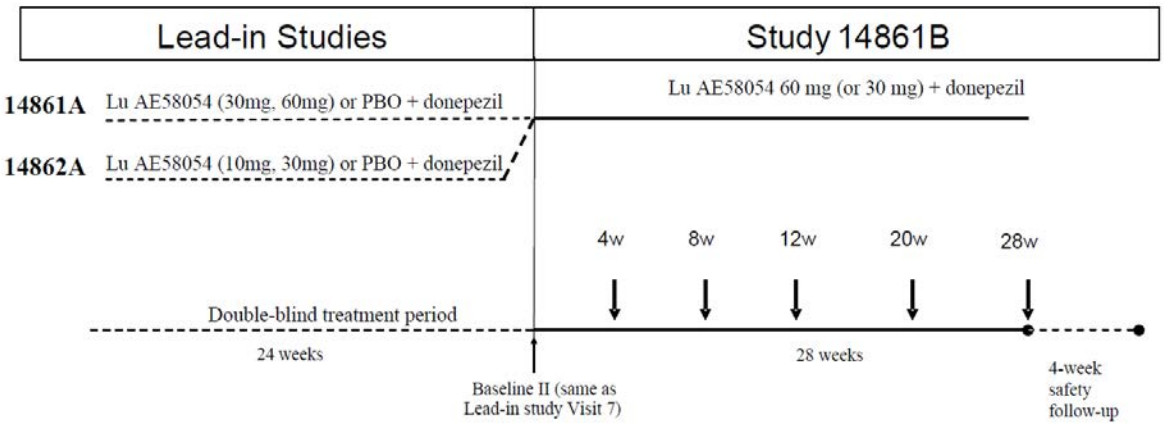
Some sites will be participating in the open-label treatment period with memantine (sub-study). In total, 100 patients who have completed the open-label treatment period will be recruited for the for the memantine sub-study. For these patients, the study will include two consecutive periods:

- *Open-label treatment period (initial 28-week period):* 28-weeks with idalopirdine 60 mg/day as adjunctive treatment to donepezil (10 mg/day). The dose of idalopirdine can be decreased to 30 mg/day if 60 mg/day is not well tolerated in the opinion of the investigator. The Baseline Visit of this period (Baseline II) will be the same visit as Visit 7 (Completion Visit) in the lead-in studies.
- *Open-label treatment period with memantine (sub-study):* 24-weeks with idalopirdine 60 mg/day (or 30 mg/day) [continuation of dose used in open-label treatment period] as adjunctive treatment to donepezil hydrochloride 10 mg/day and memantine (patient's individualised maintenance dose, including a titration phase of up to 3 weeks). Memantine should be prescribed according to investigator's judgement and the initial dose may be changed at any time throughout the course of the study, if clinically indicated in the opinion of the investigator. The Baseline Visit of this period (Baseline III) will be the same visit as Visit 6 in the open-label treatment period.

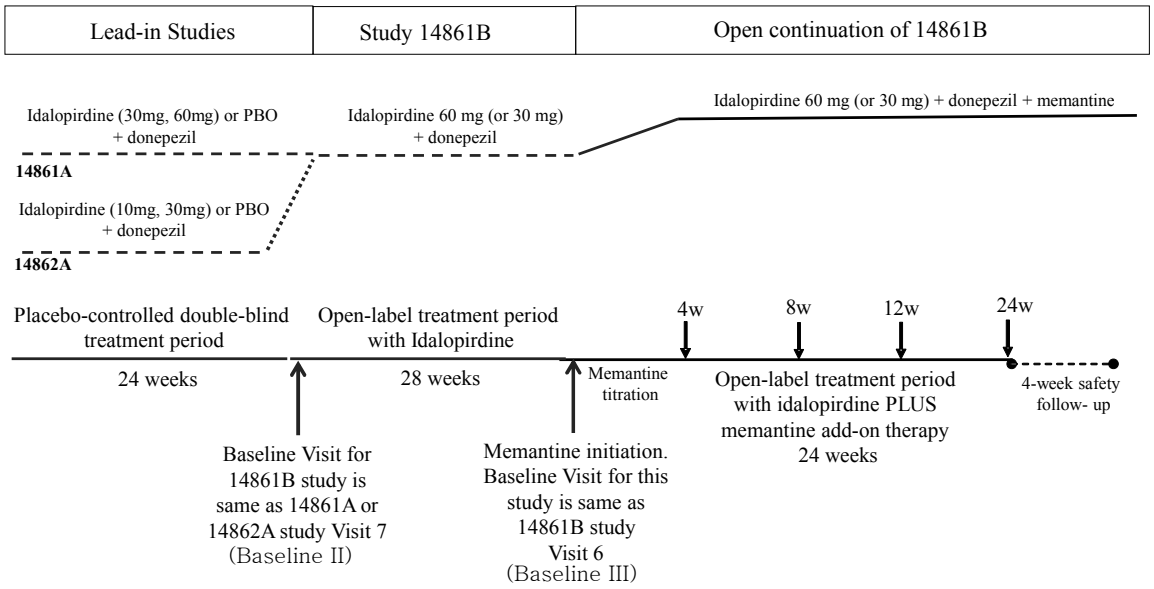
Patients completing the two consecutive treatment periods will enter a 4-week safety follow-up period. Thus the total study duration per patient in the sub-study from Baseline II to the end of the follow-up will be approximately 56 weeks.

The study design is presented in Panel 1 and Panel 2 and the scheduled assessments are summarised in Appendix II.

Panel 1 Study Design: Open-label treatment period



Panel 2 Study Design: Open-label treatment period with memantine



3 Endpoints

Secondary efficacy enpoints in the open label treatment period

- Change from Baseline I to week 52 (extension week 28) in Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) total score
- Change from Baseline II to week 52 (extension week 28) in ADAS-cog total score
- Alzheimer's disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) at week 52 (extension week 28)
- Change from Baseline I to week 52 in Change from baseline to Week 24 (extension week 28) in Alzheimer's disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL_{23}) total score
- Change from Baseline II to week 52 (extension week 28) in ADCS-ADL_{23} total score
- Change from Baseline I to week 52 (extension week 28) in Neuropsychiatric Inventory (NPI) total score and NPI single items
- Change from Baseline II to week 52 (extension week 28) in NPI total score and NPI single items
- Change from Baseline I to week 52 (extension week 28) in Mini Mental State Examination (MMSE) total score
- Change from Baseline II to week 52 (extension week 28) in MMSE total score

Secondary efficacy enpoint in the open label treatment period with memantine

- Change from Baseline III to week 24 in MMSE total score

Safety endpoints

- Adverse events (AEs)

- Clinical safety laboratory tests
- Vital signs
- Weight
- Electrocardiograms (ECGs)
- Columbia Suicide Severity Rating Scale (C-SSRS)

Other endpoints
- Plasma concentrations of idalopirdine and memantine in the open label treatment period with memantine

4 Analysis Sets

The following analysis set will be used to analyse and present data:

The sets of patients to be analysed are defined as follows:

Open label treatment period
- *all-patients-enrolled* set (APES) – all patients enrolled in the open-label treatment period
- *all-patients-treated set* (APTS) – all patients in APES who took at least one dose of IMP in the open-label treatment period

Open label treatment period with memantine
- *all-patients-enrolled set 2* (APES2) – all patients who enrolled in the open-label treatment period with memantine
- *all-patients-treated set 2* (APTS2) – all patients in APES2 who took at least one dose of IMP or memantine in the open-label treatment period with memantine.

Each patient will be classified according to these definitions based on information in data, and no Classification Meeting will be held.

If not otherwise specified, tables, figures, and listings will be based on the APTS for the open-label treatment period, and on APTS2 for the open-label treatment period with memantine.

5 Descriptive Statistics

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

Tables and figures for the open label treatment period will be presented by lead-in treatment group and in total.

Unless otherwise specified, data listings will include lead-in treatment group (placebo or idalopirdine [dose 10mg, 30mg, or 60mg]), site, patient screening number (from lead-in study), and lead-in study-Baseline I information on sex, age, race, and weight.

6 Patient Disposition

6.1 Summary of Patient Disposition

Patient disposition in the open label-treatment period will be summarised by lead-in study and in total, and include the number of patients in each analysis set defined for the period, and the number of patients in the APTS who completed or withdrew from treatment. The corresponding summary will be generated for the open-label treatment period with memantine for the total study.

6.2 Withdrawal

The number of patients who withdrew from the open-label treatment period will be summarised by primary reason for withdrawal as well as by all reasons for withdrawal.. Similar summaries will be created for the open-label treatment period with memantine. The summaries will also be presented by lead-in study for the open-label treatment period.

Patients who withdrew from treatment during the open-label treatment period will be listed and the listing will include the number of days on idalopirdine in the open-label treatment period, the primary reason for withdrawal from treatment, and all reasons for withdrawal from treatment. A similar listing will be created for patients who withdrew from treatment during the open-label treatment period with memantine.

7 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics at Baseline I will be summarised for patients in the APTS and the APTS2.

Demographics (sex, age, ethnicity, and race), patient characteristics (weight, height, BMI), and efficacy variables at Baseline I will be summarised.

Past and concurrent medical, neurological, and psychiatric disorders at the lead-in study Screening Visit (coded using the Medical Dictionary for Regulatory Activities [MedDRA], Version 19.0 or later), will be summarised.

The summaries will also be presented by lead-in study for the APTS.

8 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the WHO Drug Dictionary (WHO-DDE), version WHO ATC MAR16. , and summarised by anatomical therapeutic chemical (ATC) code, and generic drug name.

For the open label treatment period summaries will be prepared for:

- Concomitant medication continued after Baseline II
- concomitant medication started after Baseline II and at or before Baseline III for patients in APES2

For the open label treatment period with memantine summaries will be prepared for;

- concomitant medication continued after Baseline III
- concomitant medication started after Baseline III

A listing will be created that includes information about memantine dosages over the course of the open label treatment period with memantine.

9 Exposure

Exposure to IMP in this study will be defined as:

date of last dose of IMP – date of first dose of IMP + 1

For details about handling of missing IMP start or stop date, see section 18.4.1 (IMP start and stop date)

Exposure to IMP in each treatment period will be summarised using descriptive statistics, and include the patient years of exposure (PYE). PYE will be calculated as the sum of the number of days of exposure to IMP for each patient, divided by 365.25 days.

In addition, exposure to IMP in each treatment period will be categorised into day intervals. The intervals for the open-label treatment period are the following: (1 –28 [0 - 1 month], 29 – 56 [1 – 2 months], 57 – 84 [2 – 3 months], 85 – 126 [3 – 4.5 months], 127 – 168 [4.5 - 6 months], 169 – 252 [6 – 9 months]. The intervals for the open-label treatment period with memantine are the following: (1 – 168 [0 – 6 months], 169 – 252 [6 – 9 months], 253 – 364 [9 – 12 months], 365– 448 [12 – 15 months]). Missing values of exposure will not be imputed.

Number and percentage of patients with dose reduction of IMP to 30 mg/day in the open-label treatment period will be summarised. The mean dose of IMP will be calculated for each patient and summarised (mean, median, and lower and upper quartiles). Categorical summaries of patients' dosage at each visit will be presented as well.

10 Efficacy

10.1 General Efficacy Analysis Methodology

All analyses will be performed by lead-in study.

For the open label treatment period, absolute scores, change from Baseline I scores, and change from Baseline II scores for the efficacy variables will be summarised by visit week. The summaries of absolute scores and change from Baseline I scores will include data from the lead-in study and the open-label treatment period.

For the open label treatment period with memantine, absolute score and change from Baseline Baseline III in MMSE total score will be summarised by visit week.

All the p-values will be based on two-sided tests; the confidence intervals (CIs) will be two-sided.

Nominal p-values will be presented together with nominal 95% CIs.

10.2 Exploratory Analysis of Efficacy

Changes from baseline I in ADAS-Cog total score, ADCS-ADL_{23} total score, NPI total score, NPI individual items, and MMSE total score will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. Baseline will be defined as the baseline in the lead-in study (Baseline I). The model will include data from visits in both the lead-in study and the open label treatment period. The model will include the fixed categorical effects of treatment group in the lead-in study, country, visit week, treatment-by-week interaction, MMSE-stratum (<19, ≥ 19) at baseline I, and MMSE-stratum at baseline I-by-visit interaction and the continuous covariates of baseline score and baseline score-by-visit interaction.

In all analyses, an unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be based on the missing-at-random (MAR) assumption and performed using all available observations (observed cases [OC] data).

Line plots will be created to illustrate the MMRM estimates of least squares means by visit week. ADCS-CGIC will be analysed using the same methodology, using the scores at each visit and the ADCS-CGIC score at Baseline I in the lead-in study as baseline.

11 Safety

11.1 Adverse Events

11.1.1 General Methodology for Adverse Events

The tables for the open label treatment periodwill be sorted in descending order by the percentage of patients in the lead-in IDL 60 mg group. Unless otherwise specified, the summaries of adverse events will include the total number and percentage of patients with an adverse event. For sex-specific preferred terms, the denominator in the % calculations will be the number of patients of that sex. Sex-specific preferred terms will be marked in the summaries.

In summaries of adverse events presented by intensity, the maximum intensity of the adverse event in the treatment period will be used for patients who have more than one intensity of that event. Adverse events for which information on intensity is missing will be classified as *severe*.

Listings of adverse events will be sorted by lead-in study treatment group, site, patient screening number (from lead-in study), and adverse event start date and include preferred term, investigator term, adverse event start date, days since first dose of IMP in the treatment period, duration of the adverse event in the treatment period, date of death, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included.

11.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 19.0, or later.

11.1.3 Classification of Adverse Events

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

treatment-emergent adverse event (TEAE) – an adverse event that starts or increases in intensity after the date of Baseline II.

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

11.1.4 Allocation of TEAEs to Treatment Periods

TEAEs will be allocated to treatment periods according to the time of onset of the adverse event:

- *adverse event in the open-label treatment period* – an adverse event that starts or increases in intensity after the date of Baseline II and at or before the date of the last protocol-

specified contact in the study for patients not continuing into the open-label treatment period with memantine, and at or before the date of Baseline III for patients in the APES2.
- *adverse event in the open-label treatment period with memantine* – an adverse event that starts or increases in intensity after the date of Baseline III and at or before the date of the last protocol-specified contact in the study.

Note, the completion Visit in the lead-in studies are the same as the Baseline II Visit in the extension study, and adverse events ongoing or starting at Baseline II and not increasing intensity will only be reported in the lead-in study.

All tables and listings will be presented separately for adverse events in the open label treatment period, and the open label treatment period with memantine.

11.1.5 All Adverse Events

All adverse events will be listed for the APES and APES2.

An overview of the PYE, numbers, and percentages of patients with TEAEs, serious adverse events (SAEs), adverse events leading to withdrawal, or patients who died will be provided. For TEAEs, SAEs, and adverse events leading to withdrawal, the total number of events will be included.

11.1.6 Treatment-emergent Adverse Events

The following summaries will be provided:
- TEAEs by SOC and preferred term (only for open label treatment period)
- TEAEs by preferred term
- TEAEs with an incidence >3% by preferred term
- causally related TEAEs by SOC and preferred term TEAEs by intensity (*mild*/*moderate*/*severe)* and preferred term
- causally related TEAEs by intensity and preferred term (only for open label treatment period)

11.1.7 Deaths

All adverse events for patients who died will be listed.

11.1.8 Serious Adverse Events

All SAEs will be listed.

Treatment-emergent SAEs will be summarised by preferred term. For the open label treatment period the summary will also be generated by SOC and preferred term.

11.1.9 Adverse Events Leading to Withdrawal

All adverse events leading to withdrawal will be listed.

TEAEs leading to withdrawal will be summarised by preferred term. For the open label treatment period the summary will also be generated by SOC and preferred term.

11.1.10 Adverse Events Leading to Dose Reduction of IMP

Adverse events leading to dose reduction of idalopirdine in the open label treatment period will be listed.

Adverse events leading to dose reduction of idalopirdine in the open label treatment period will be summarised by preferred term.

11.1.11 Adverse Events of Special Interest

The following standardized MedDRA queries (SMQ) will be summarised in total and by preferred term:

- Convulsions (narrow scope)
- Drug-related hepatic disorders -comprehensive search
- Haemorrhages (broad scope)

11.2 General Methodology for Other Safety Data

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

Descriptive statistics for the safety variables in the open label treatment period, absolute values changes from both Baseline I and Baseline II, will be presented by visit and the last post-baseline assessment in the treatment period.

For the open-label treatment period with memantine, summaries will be presented for absolute values and change from Baseline III by visit and last assessment in the treatment period .

The number and percentage of patients with at least one PCS value at any post-Baseline II assessment in the open-label treatment period will be summarised by variable. The number and percentage of patients with at least one PCS value at any post-Baseline III assessment in the open-label treatment period with memantine will be summarised by variable . All available assessments will be included in the evaluation of PCS values (scheduled, re-assessments, and unscheduled). For tests where PCS is defined as a change, the summaries will be prepared both for PCS compared to baseline I and baseline II for the open label treatment period.

For patients with post-baseline II PCS values (compared to baseline II) in the open-label treatment period, listings will be provided including all available values for the variable, with

flagging of PCS values and out-of-reference-range values. The corresponding listings will be prepared for the open label treatment period with memantine.

All adverse events for patients with post-baseline II PCS value (compared to baseline II) in the open-label treatment periods will be listed by lead-in treatment group and patient screening number and include the PCS value; investigator term and preferred term for the adverse event; and intensity, seriousness, causality, action taken, outcome, start date, and duration of the adverse event; and days since first dose of IMP at the time of onset of the adverse event. The PCS value will be listed next to any adverse events occurring in the same visit window; the PCS values and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event. The corresponding listings will be presented for the open-label treatment period with memantine.

11.3 Clinical Safety Laboratory Test Data

11.3.1 Data Presentation

The PCS criteria for the clinical safety laboratory tests are in Table 1.

All the clinical safety laboratory test values will be presented in conventional and/or Système International (SI) units.

The summary statistics for GGT, ALT, AST, ALP, Bilirubin, and eosinophils will be presented in a separate tables, including worst (highest) post-Baseline II assessment during the open-label treatment period or post-Baseline III assessment during the open-label treatment period with memantine. All available assessments will be included in the evaluation of the worst assessment.

Graphical presentations of gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin (BILI) are described Panel 3 (further graphical presentations of ALT, AST, ALP, and BILI will be done in the evaluation of drug-induced liver injury).

Panel 3 Graphical Presentations for the Liver Function Tests

Laboratory Test	Measure	Patient Selection	Line Plot
Open-label treatment period			
GGT	Absolute measure	Patients with a post-Baseline II value of GGT ≥200	√
ALT	Absolute measure	Patients with a post-Baseline II value out of upper reference range for ALT	√
AST	Absolute measure	Patients with a post-Baseline II value out of upper reference range for AST	√
ALP	Absolute measure	Patients with a post-Baseline II value out of upper reference range for ALP	√
BILI	Absolute measure	Patients with a post-Baseline II value out of upper reference range for BILI	√
Open-label treatment period with memantine			
GGT	Absolute measure	Patients with a post-Baseline III value of GGT≥200	√
ALT	Absolute measure	Patients with a post-Baseline III value out of upper reference range for ALT	√
AST	Absolute measure	Patients with a post-Baseline III value out of upper reference range for AST	√
ALP	Absolute measure	Patients with a post-Baseline III value out of upper reference range for AP	√
BILI	Absolute measure	Patients with a post-Baseline III value out of upper reference range for BILI	√

11.3.2 Urinalysis

For tests based on urine dipsticks, the results are categorical, and the number and percentage of patients will be summarised for each test by visit week and last assessment in each treatment period.

11.3.3 Evaluation of Potential Drug-induced Liver Injury (DILI)

Signals of DILI post-Baseline II for the open label treatment period and post Baseline III for the open label treatment period with memantine will be assessed according to the FDA guideline[1], as well as by using additional criteria, as described below:

The number and percentage of patients post-Baseline II/Baseline III in the categories below for AST/ALT, and AST and ALT separately will be summarised:

- ULN < value ≤ 1.5xULN
- 1.5xULN < value ≤2xULN
- 2xULN < value ≤ 3xULN
- 3xULN < value ≤ 5xULN
- 5xULN < value ≤ 10xULN
- 10xULN < value ≤ 20xULN

- 20xULN < value

The number and percentage of patients post-Baseline II/Baseline III in the categories below for ALP and Bilirubin will be summarised:

- ULN<value ≤1.5xULN
- 1.5xULN< value ≤2xULN
- 2xULN< value ≤3xULN
- value >3xULN

In the summaries, each patient should be counted only once using the worst post-Baseline II/Baseline III assessment.

The cumulative number and percentage of patients post-baseline in the categories will also be summarised for each treatment period.

Number and percentage of patients fulfilling the joint criteria below post-baseline II/Baseline III will be summarised:

- (PEAK AST OR PEAK ALT>3xULN) AND PEAK BILI>2xULN AND PEAK ALP>1.5xULN
- (PEAK AST OR PEAK ALT>3xULN) AND PEAK BILI>2xULN AND PEAK ALP≤1.5xULN
- PEAK GGT>200 (IU/L) without (PEAK AST OR PEAK ALT OR PEAK ALP>2xULN)
- Number and percentage of patients with a post-Baseline II /Baseline III value ≥5% for B-eosinophils/leukocytes (ESOLE) will be summarised.

Evaluation of potential Drug-Induced Serious Hepatotoxicity (eDISH) will also be done by plots. Scatter plots of peak ALT/AST versus peak BILI in the treatment period (note that this means that the peak ALT/AST and the peak BILI may not occur at the same assessment time-point). The values will be normalised by the ULN (unit xULN) and the X and Y-axes will be on log scale. The plot will include a reference line for ALT/AST values >3xULN, and a reference line for BILI values>2xULN. Four quadrants are defined by the reference lines, where the right upper quadrant being the most specific indicator for a drug's potential for causing serious liver injury (Hy's law quadrant). The plot will include number of patients in each quadrant.

Subject line plots with values-by-time for ALT, AST, ALP , Bilirubin, eosinophils, and GGT (overlaid in the same plot) will be generated for patients with ALT/AST > 1xULN post-baseline II/Baseline III. The test values will be normalised by the ULN (unit xULN) and the Y-axis will be on log scale. The time will be days since Baseline II/Baseline III, and reference lines for the day of first-and last IMP intake in the treatment period will be included. All assessments will be included. If there is more than one assessment at the same time point for a test, the maximum value will be used. A corresponding plot will be generated for patients with ALT/AST > 3xULN post-baseline I in the lead-in study or the open-label treatment period, where values in the lead-in treatment period and the open-label treatment will be included.

Conditional correlations of values adjusted for patient average level (mean value for each patient within each treatment period subtracted from the subject values at each visit within the treatment period) of ALT, AST, ALP, and bilirubin versus eosinophils will be generated as tables and scatter plots for:

- All patients
- Patients with a post-baseline II/Baseline III value of ALT/AST>2xULN
- Patients with a post-baseline II/Baseline IIIvalue of ALT/AST>3xULN

Patients in the APTS with a post-Baseline II/Baseline III value of GGT, ALT, AST, ALP, bilirubin, >1xULN will be listed, and the listing will include all available ALT, AST, BILI, ALP, GGT, and EOSLE values, sorted by completion/withdrawal status, treatment group, site, subject number, assessment date and time.

11.4 Vital Signs and Weight

The PCS criteria for vital signs and weight are in Table 2.

An overview of the graphical presentations is provided in Panel 4.

Panel 4 Graphical Presentations for Vital Signs and Weight

Variable	Measure	Patient Selection	Line Plot
Weight	Absolute value	Patients with a post-Baseline II PCS Low Value Compared to Baseline I in the open label treatment period	√
Weight	Absolute value	Patients with a post-baseline II PCS Low Value Compared to Baseline II in the Open-label Treatment Period	√
Weight	Absolute value	Patients with a post-baseline III PCS Low Value Compared to Baseline I	√
Weight	Absolute value	Patients with a post-baseline III PCS Low Value Compared to Baseline III	√

11.5 ECGs

The PCS criteria for the ECG parameters are in Table 3.

An overview of the graphical presentations for the ECG parameters is provided in Panel 5.

Panel 5 Graphical Presentations for ECG Parameters

Parameter	Measure	Patient Selection	Line Plot
Heart ate	Absolute value	Patients with a post-Baseline II PCS value compared to Baseline I in the open label treatment period	√
Heart ate	Absolute value	Patients with a post-Baseline II PCS value compared to Baseline II in the open label treatment period	√
QTcF	Absolute value	Patients with a post-Baseline II PCS value compared to Baseline I in the open label treatment period	√
QTcF	Absolute value	Patients with a post-Baseline II PCS value compared to Baseline II in the open label treatment period	√
Heart rate	Absolute value	Patients with a post-Baseline III PCS value compared to Baseline I	√
Heart rate	Absolute value	Patients with a post-Baseline III PCS value compared to Baseline III	√
QTcF	Absolute value	Patients with a post-Baseline III PCS value compared to Baseline I	√
QTcF	Absolute value	Patients with a post-Baseline III PCS value compared to Baseline III	√

11.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

For all visits, the C-SSRS was assessed using the Since Last Visit Version that collects information for a pre-specified, limited period.

The C-SSRS scores will be summarised (as described below) for open-label treatment period and open label treatment period with memantine for patients with at least one post-Baseline II/Baseline III, regardless of whether they had a Baseline II/Baseline III assessment.

Missing C-SSRS scores will not be imputed.

The C-SSRS items are described in Panel 6. Patients with *no suicidal ideation or behaviour* are those who answered "No" to all items for *suicidal ideation* and *suicidal behaviour*. For each evaluation (baseline II and post-baseline II for the open label treatment period, and baseline III, and post-baseline III for the open-label treatment period with memantine), the most severe event per patient related to *suicidal ideation* and *suicidial behaviour* will be summarised.

In the C-SSRS, *non-suicidal self-injurious* behaviour is captured as a different behaviour, and regarded independently of reported *suicidal ideation* and *suicidal behaviour* events. Positive responses to *non-suicidal self-injurious behaviour* will be summarised.

Panel 6 C-SSRS Scores

aCRF Item	Description
	Suicidal Ideation
CSSRS01	Wish to be dead
CSSRS02	Non-specific active suicidal thoughts
CSSRS03	Active suicidal ideation with any methods (not plan) without intent to act
CSSRS04	Active suicidal ideation with some intent to act, without specific plan
CSSRS05	Active suicidal ideation with specific plan and intent
	Suicidal Behaviour
CSSRS25	Preparatory acts or behaviour
CSSRS23	Aborted attempt
CSSRS21	Interrupted attempt
CSSRS18	Non-fatal suicide attempt
CSSRS27	Completed suicide (only applicable for the post-baseline assessments)
	Self-Injurious Behaviour Without Suicidal Intent
CSSRS20	Non-suicidal, self-injurious behaviour

For patients with any post-baseline II/baseline III suicidal behaviour (C-SSRS scores of 6 to 10) or ideation (C-SSRS scores of 1 – 5), listings will be prepared including all C-SSRS scores; C-SSRS scores related to suicidal behaviour or ideation will be flagged.

12 Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentrations of idalopirdine and memantine will be summarised descriptively for the APTS2 in the open-label treatment period with memantine.

13 Health Economic Analyses

The health economic assessments conducted during the open-label treatment period (RUD Lite, EQ-5D-3L and Dependence scale) in the open-label will be summarised by lead-in study. For the open label treatment period, absolute scores, change from Baseline I scores, and change from Baseline II will be summarised by visit week. The summaries of absolute scores and change from Baseline I scores will include data from the lead-in study and the open-label treatment period.

For the open label treatment period with memantine, absolute score and change from Baseline III in MMSE total score will be summarised by visit week.

14 Interim Analyses

No interim analyses planned.

15 Sample Size Considerations

Open-label treatment period:

The study will include eligible patients who have completed Visit 7 (Completion Visit) of the lead-in studies. Assuming a completion rate of 85% and that approximately 85% of these are eligible and complete the extension study, this results in a total of approximately (3x310 + 3x280) x 85% x 85% ≈ 1280 patients completing this study.

Open-label treatment period with memantine (sub-study):

With a sample size of n=100 the upper 1-sided 90% confidence limit for 0 to 10 AEs observed is:

Number of AEs observed	0	1	2	3	4	5	10
Upper 1-sided CI for AE incidence	2.3%	3.9%	5.3%	6.6%	7.9%	9.1%	15.0%

This is regarded as sufficient accuracy for evaluating safety and tolerability.

16 Data and Analysis Standards and Statistical Software

The data will be collected and analysed in accordance with the Lundbeck standards specified in Lundbeck SDTM, Version 3.1.2 or later, SADs, Version 5.1 or later, and TGML, Version 7.0 or later.

The statistical software used will be SAS®, Version 9.4 or later.

17 Changes to Analyses Specified in the Protocol

C-SSRS will be summarized as worst case per treatment period rather than worst case per visit. However, all C-SSRS results for the study will be listed for those patients that experience any suicidal ideation or behaviour.

18 Details on Data Handling

18.1 Definition of Baseline

The Baseline I value will be defined as the value captured either at the Screening Visit or the Baseline Visit of the lead-in study, whichever comes later.

Unless otherwise specified, the Baseline II Visit is the same as the Completion Visit (Visit 7/Week 24) in the lead-in studies (14861A and 14862A).

Baseline III is the same as the Completion Visit (Visit 6/Week 28) of the open-label treatment period.

18.2 Derived Variables

18.2.1 MMSE Total Score and MMSE Stratum

MMSE consists of 8 subcategories (orientation to time, orientation to place, registration, attention and calculation, recall, language, repetition, and complex commands), with in total 30 questions recording correct/incorrect responses (coded 1/0). The MMSE total score is defined as the sum of the 30 questions and the total score ranges from 0 to 30 (at screening 12 to 22 due to inclusion criterion), with a lower scores meaning more severe dementia.

The subcategory *attention and calculation* consists of 5 questions (aCRF items MMSE04A to MMSE04E), where the patient continuously should subtract 7 from 100 (correct responses 93, 86, 79, 72, and 65). If a question is answered incorrectly and the subsequent questions not are recorded, the missing responses will be counted as incorrect (0).

The total score will be missing if three or more items scores are missing, and if less than three item scores are missing the missing item scores will be imputed by the worst case (0).

MMSE stratum (mild, MMSE total score ≥19; moderate, MMSE total score <19) used in the analyses will be based on the assessment collected at the lead-in study screening visit.

18.2.2 ADAS-Cog Total Score

The ADAS-Cog assess the patient's orientation, memory (word recall, recognition, and remembering instructions), language (spoken language ability, comprehension of the spoken language, word finding difficulty, naming objects and fingers, following commands), and praxis (ideational and constructional). The ADAS-Cog total score is defined as the sum of the 11 item scores described in Panel 7. If three or more items scores are missing, the total score will be missing. If less than three item scores are missing the missing item scores will be imputed by the worst score for the item.

The ADAS-Cog total score ranges from 0 to 70, with a lower score indicating a lower cognitive impairment.

Panel 7 Definition of ADAS-Cog Item Scores

ADAS-Cog Item	Data collected in the eCRF (aCRF variable name)	Defintion of ADAS-Cog Item Scores used in the calculation of the total score (SADs paramcd name)
1. Word recall task	Total number of word recalled **correctly**, recorded in three trials (ranges 0-10 in each trial): ADCOG01 ADCOG02 ADCOG03	Average of the total number of words recorded incorrectly in the three trials rounded to the closest integer with .5 rounded upwards (ranges from 0-10): ACITM01=round(((10- ADCOG01)+(10- ADCOG02)+(10- ADCOG03))/3,1.); If <3 of the eCRF scores are missing, the item score will be the average of the available scores.
2. Naming task	Total number of object/fingers named **correctly** (ranges 0-17) ADCOG05	eCRF score converted to total number of object/fingers named incorrectly (17-ADCOG05), and then classified according to the scoring scheme below (ranges 0-5): ACITM02= 0 = 0 – 2 1 = 3 – 5 2 = 6 – 8 3 = 9 – 11 4 = 12 – 14 5 = 15 – 17
3. Commands	Total number of commands performed **correctly** (ranges 0-5): ADCOG07	eCRF score converted to total number of commands performed incorrectly (ranges 0-5): ACITM03=5- ADCOG07;
4. Constructional praxis	Total number of drawings performed **incorrectly** (ranges 0-5): ADCOG08	ACITM04= ADCOG08
5. Ideational praxis	Total number of steps completed **correctly** (ranges 0-5): ADCOG09	eCRF score converted to total number of steps completed incorrectly (ranges 0-5): ACITM05=5- ADCOG09;
6. Orientation	Total number of items answered **correctly** (ranges 0-8): ADCOG10	eCRF score converted to total number of items answered incorrectly (ranges 0-8): ACITM06=8- ADCOG10;
7. Word recognition task	Total number of words identified **correctly** and total number of words identified **incorrectly** (both scores ranges 0-12):	Total number of words identified **incorrectly**, where scores>12 truncated to 12 (ranges 0-12):

	ADCOG11 ADCOG12	ACITM07= Min((12- ADCOG11)+ ADCOG12, 12); If ADCRGT01 or ADCRGT02 is missing, the item score will be missing
8. Remembering test instructions	Level of impairment (ranges 0-5, see category labels below): ADCOG14 0 = None 1 = Very Mild 2 = Mild 3 = Moderate 4 = Moderately Severe 5 = Severe	ACITM08= ADCOG14
9. Language	Level of impairment (ranges 0-5, same category labels as for item 8): ADCOG15	ACITM09= ADCOG15
10. Comprehension of spoken language	Level of impairment (ranges 0-5, same category labels as for item 8): ADCOG16	ACITM10= ADCOG16
11. Word finding difficulty	Level of impairment (ranges 0-5, same category labels as for item 8): ADCOG17	ACITM11= ADCOG17

18.2.3 ADCS-ADL$_{23}$ Total Score

The ADCS-ADL$_{23}$ scale contains of 23 item scores (See Panel 8), where each item contains one or more questions.

The ADCS-ADL$_{23}$ total score is defined as the sum of the 23 item scores. “Don’t know” responses will be counted as worst case (0). For patients institutionalized, item score number 18 (Left On His/Her Own) will be counted as worst case (0). The scoring scheme for the item scores are described in Panel 8.

Panel 8 ADCS-ADL$_{23}$ Items

ADCS-ADL$_{23}$ Item	**Data collected in the eCRF (aCRF variable name)**	**Defintion of ADCS-ADL$_{23}$ Item Scores used in the calculation of the total score (SADs paramcd name)**
1. Usual Eating Performance	ADADL01	Item score ranges 0-3: ADL01=ADADL01
2. Optimal Walking Performance	ADADL02	Item score ranges 0-3: ADL02=ADADL02
3. Usual Bowel/Bladder Function	ADADL03	Item score ranges 0-3: ADL03=ADADL03
4. Usual Bathing Performance	ADADL04	Item score ranges 0-3: ADL04=ADADL04
5. Optimal Grooming Performance	ADADL05	Item score ranges 0-3: ADL05=ADADL05
6. Dressing	ADADL06 ADADL07 ADADL08	Item score ranges 0-7: If ADADL06=”No” or ADADL06=”Don’t know” then ADL06=0; else if ADADL06=”Yes” then ADL06= ADADL07; ADL06=ADL06+ADADL08;
7. Use a Telephone	ADADL09 ADADL10	Item score ranges 0-5: If ADADL09=”No” or ADADL09=”Don’t know” then ADL07=0; else if ADADL09=”Yes” then ADL07= ADADL10;
8. Watch Television	ADADL11 ADADL12 ADADL13 ADADL14	Item score ranges 0-3: if ADADL11=”No” or ADADL11=”Don’t know” then ADL08=0; %**“Yes”/”No”/”Don’t know” counted as 1/0/0; else if ADADL11=”Yes” then ADL08= ADADL12+ADADL13+ ADADL14;

9. Pay Attention to Conversation	ADADL15 ADADL16	Item score ranges 0-3: If ADADL15=”No” or ADADL15”Don’t know” then ADL09=0; else if ADADL15=”Yes” then ADL09= ADADL16;
10. Clear Dishes	ADADL17 ADADL18	Item score ranges 0-3: If ADADL17=”No” or ADADL17=”Don’t know” then ADL10=0; else if ADADL17=”Yes” then ADL10= ADADL18;
11. Find Belongings	ADADL19 ADADL20	Item score ranges 0-3: If ADADL19=”No” or ADADL19=”Don’t know” then ADL11=0; else if ADADL19=”Yes” then ADL11= ADADL20;
12. Obtain Beverage	ADADL21 ADADL22	Item score ranges 0-3: If ADADL21=”No” or ADADL21=”Don’t know” then ADL12=0; else if ADADL21=”Yes” then ADL12= ADADL22;
13. Make a Meal	ADADL23 ADADL24	Item score ranges 0-4: If ADADL23=”No” or ADADL23=”Don’t know” then ADL13=0; else if ADADL23=”Yes” then ADL13= ADADL24;
14. Dispose of Garbage	ADADL25 ADADL26	Item score ranges 0-3: If ADADL25=”No” or ADADL25=”Don’t know” then TADL14=0; else if ADADL25=”Yes” then ADL14= ADADL26;
15. Get Around Outside Home	ADADL27 ADADL28	Item score ranges 0-4: If ADADL27=”No” or ADADL27=”Don’t know” then ADL15=0; else if ADADL27=”Yes” then ADL15= ADADL28;

16. Go Shopping	ADADL29 ADADL30 ADADL31	Item score ranges 0-4: If ADADL29=”No” or ADADL29=”Don’t know” then ADL16=0; %**“Yes”/”No”/”Don’t know” counted as 1/0/0 (ADADL31); else if ADADL29=”Yes” then ADL16= ADADL30+ ADADL31;
17. Keep Appointments	ADADL32 ADADL33	Item score ranges 0-3: If ADADL32=”No” or ADADL32=”Don’t know” then ADL17=0; else if ADADL32=”Yes” then ADL17= ADADL33;
18. Left On His/Her Own	ADADL34 ADADL35 ADADL36 ADADL37 ADADL38	Item score ranges 0-3: If ADADL34=”Checked” then ADL18=0; else if ADADL35=”No” or ADADL35=”Don’t know” then ADL18=0; %**“Yes”/”No”/”Don’t know” counted as 1/0/0; else if ADADL35=”Yes” then ADL18= ADADL36+ ADADL37+ ADADL38;
19. Talk About Current Events	ADADL39 ADADL40 ADADL41 ADADL42	Item score ranges 0-3: if ADADL39=”No” or ADADL39=”Don’t know” then ADL19=0; %**“Yes”/”No”/”Don’t know” counted as 1/0/0; else if ADADL39=”Yes” then ADL19= ADADL40+ ADADL41+ ADADL42;
20. Read More Than 5 Minutes	ADADL43 ADADL44 ADADL45	Item score ranges 0-2: if ADADL43=”No” or ADADL43=”Don’t know” then ADL20=0; %**“Yes”/”No”/”Don’t know” counted as 1/0/0; else if ADADL43=”Yes” then ADL20= ADADL44+ ADADL45;
21. Write Things Down	ADADL46 ADADL47	Item score ranges 0-3: If ADADL46=”No” or ADADL46=”Don’t know” then ADL21=0; else if ADADL46=”Yes” then ADL21= ADADL47;

22. Perform Pastime	ADADL48 ADADL49	Item score ranges 0-3: If ADADL48=”No” or ADADL48=”Don’t know” then ADL22=0; else if ADADL48=”Yes” then ADL22= ADADL49;
23. Use Household Appliance	ADADL50 ADADL51	Item score ranges 0-4: If ADADL50=”No” or ADADL50=”Don’t know” then ADL23=0; else if ADADL50=”Yes” then ADL23= ADADL51;

If five or more items scores are missing, the total score will be missing. If less than five item scores are missing, the missing questions within the item score will be imputed by the worst case for each missing question (missing main responses will be imputed by 0; if the main response equal to “Yes”, missing subsequent question(s) will be imputed by the worst score for each question).

The ADCS-ADL_{23} total score ranges from 0 to 78, with a higher score indicating a higher functioning status.

18.2.4 NPI Total Score and Individual Items

The NPI scale consists of 12 domains (Delutions, Hallucinations, Agitation/Aggression, Depression/Dysphoria, Anxiety, Elation/Euphoria, Apathy/Indifference, Disinhibition, Irritability/Lability, Aberrant Motor Behaviour, Sleep, and Appetite and Eating Disorders). The NPI total score is defined as the sum of the 12 domain scores, where the domain score for each domain is calculated as (the domain is given by category 1-12 in the aCRF variable NPI01):

- If status (aCRF NPI02) is equal to “Not Applicable” or “No”, the NPI domain score will be equal to 0; otherwise, the NPI domain score will be the product of frequency (aCRF NPI03, ranging from 1 to 4), and severity (aCRF NPI04, ranging from 1 to 3).
- If four or more domain scores are missing (due to missing record in status, or missing frequency, or severity for the domain), the NPI total score will be missing. If less than four domain scores are missing, the missing doimains will in the calculation of the NPI total score be imputed by the mean of the non-missing domain scores, rounded to the closest integer (.5 rounded upwards).

Each domain score ranges from 0 to 12, and the NPI total score ranges from 0 to 144 with a higher score indicates a more serious behavioral issue.

18.3 Assigning Data to Visits

18.3.1 Rating Scales

The assessment at the Withdrawal Visit for patients withdrawn from treatment will be assigned to a nominal visit in the Treatment Period, according to the visit windowing specified in Panel 9 and Panel 10. The assessment collected at the scheduled visit will be used in the analyses, or the windowed assessment from the Withdrawal Visit if no schedule assessment is available. If the assessment at the Withdrawal Visit is assigned to the same visit as an assessment at a scheduled visit, the assessment from the scheduled visit will be used. Otherwise, the assessments at the scheduled visits will be used.

Panel 9 Visit Windows for Efficacy Assessments (open-label treatment period)

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V1 (Baseline II /Completion Visit for lead-in study)	0	0	0
V4	12	84	1 to 139
V6 (Completion/Withdrawal)	28	196	>139

MMSE is only assessed at Baseline II, Baseline III and the Completion/Withdrawal visit. As such, the visit windows for MMSE are specified in Panel 10.

Panel 10 Visit Windows for MMSE

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V1 (Baseline II /Completion Visit for lead-in study)	0	0	0
V6 (Baseline III/Completion Visit for open-label treatment period)	28	196	1 to 279
V11 (Completion Visit for open-label treatment period with memantine)	52	364	>279

18.3.2 Safety Variables

The first usable assessment at the Withdrawal Visit for safety variables (laboratory tests, vital signs, weight and ECGs) will be assigned to a nominal visit in the corresponding Treatment Period, according to the visit windowing specified in Panel 11.

For assessments at the Baseline II/III Visit, the last usable assessment will be used. For assessments at visits post-baseline, the first usable assessment from the scheduled visit will be used, or the assessment from the Withdrawal Visit will be used if no scheduled assessment is available.

Panel 11 Visit Windows for Safety Assessments

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
Open-label treatment period			
V1 (Baseline II/Completion Visit for lead-in study)	0	0	0
V2	4	28	1 to 41
V3	8	56	42 to 69
V4	12	84	70 to 111
V5	20	140	112 to 167
V6 (Completion Visit for open-label treatment period)	28	196	>167
Open-label treatment period with memantine (APTS2)			
V6 (Baseline III/Completion Visit open-label treatment period)	28	196	167 to 209
V8	32	224	210 to 237
V9	36	252	238 to 265
V10	40	280	266 to 321
V11 (Completion visit for open-label treatment period with memantine)	52	364	>321

18.4 Handling of Missing or Incomplete Dates/Times

18.4.1 IMP Start and Stop Dates

A missing IMP start date will be imputed with the date of Baseline II for patients in the APTS with an unknown IMP start date.

A missing IMP stop date will not be imputed. As such, exposure will be missing for a patient with a missing IMP stop date and the patient will contribute as having no exposure in the calculation of PYE. If it can be ascertained from other data that the patient did take IMP until a specific date, this date may be used to calculate exposure.

18.4.2 Withdrawal Date

For withdrawn patients with a missing Withdrawal Visit, the date of the last attended visit in the corresponding Treatment Period will be used in the calculation of time to withdrawal from treatment.

18.4.3 Medical Disorder Start and Stop Dates

No imputation of dates will be done.

18.4.4 Adverse Event Start and Stop Dates

If a stop date is missing due to an adverse event being on-going, the last visit date will be used as the stop date in the classification of TEAEs.

An adverse event with a missing or incomplete start or stop date will be classified as a pre-treatment adverse event if the patient was taking placebo in the lead-in study and the following conditions are met:

- The start date is missing or incomplete, and the stop date is prior to the Baseline II visit, or the stop date is incomplete but known to be prior to the Baseline II visit (stop day is missing and stop year and month are before the year and month of the Baseline II visit, or stop day and month are missing and stop year is before the year of Baseline II)
- The start date is incomplete but known to be prior to the Baseline II visit (start day is missing and start year and month are before the year and month of the Baseline II visit, or start day and month are missing and start year is before the year of the Baseline II visit), and no change in intensity

If a start date is missing for an adverse event and the stop date is prior to the Baseline II visit, then the adverse event will be regarded as starting prior to the study and will not be included in the reporting of AEs in the study. In all other instances of an adverse event with a missing start or stop date, the adverse event will be classified as a TEAE.

18.5 Grouping of Small Countries

In analyses where country is a factor, countries where not all treatment groups are represented in the APTS will be grouped according to the following stepwise procedure:

- Step 1 – All countries where not all treatment groups are represented in the APTS will be grouped into a single collective country within the same continent.
- Step 2 - If not all treatment groups are represented in the APTS for a grouped country, the countries will be grouped with the smallest country within the same continent for which all treatment groups are represented in the APTS. If there is more than one such country, the first country in ascending alphabetic order will be selected for the grouping.

References

1. United States Food and Drug Administration (FDA). Guidance for Industry: Drug-induced liver injury: Premarketing Clinical Evaluation. July 2009.

Appendix I
Statistical Analysis Plan
Authentication and Authorisation

Statistical Analysis Plan
Authentication and Authorisation

Study title:	An open-label extension study to evaluate the long-term safety and tolerability of Lu AE58054 as adjunctive treatment to donepezil in patients with mild-moderate Alzheimer's disease
SAP date:	10 July 2017

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

Authentication

Biostatistician:	[redacted]
CRS:	[redacted], CRD Neurology Idalopirdine Team

Authorisation

Head of Biostatistics:	[redacted]

Appendix II
Study Flow Chart

Study Flow Chart

Study Procedures and Assessments [open-label treatment period]

Visit	Baseline II[a]	Treatment Period				Completion/ Withdrawal[b]	Safety Follow-up[c]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day[d]/	**0**	**28/**	**56/**	**84/**	**140/**	**196/**	**224/**
End of Week		**4**	**8**	**12**	**20**	**28**	**32**
Visit Window[e] (days relative to nominal visit)		**± 7d**	**± 7d**	**± 7d**	**± 7d**	**± 7d**	**+ 7d**
Screening/Baseline Procedures and Assessments							
Signed informed consent	√						
Demographics	√[f]						
Height	√[f]						
Medical history	√[f]						
Inclusion/exclusion criteria	√						
Efficacy Assessments							
MMSE	√[g]					√	
ADAS-Cog	√[g]			√		√	
ADCS-ADL_{23}	√[g]			√		√	
ADCS-CGIC[h]	√[g]			√		√	
NPI	√[g]			√		√	
Other Assessments							
RUD Lite	√[g]			√		√	
EQ-5D-3L	√[g]			√		√	
Dependence scale	√[i]			√		√	
Safety Assessments							
Adverse events	√[j]	√	√	√	√	√	√[k]
Blood and urine sampling for clinical safety laboratory tests	√[g]	√	√	√	√	√	
Vital signs, weight, ECGs	√[g]	√	√	√	√	√	
C-SSRS	√[g]	√	√	√	√	√	
Examinations (physical, neurological)	√[g]		√		√	√	
Other Study Procedures							
IMP and donepezil[l] hydrochloride dispensed	√	√	√	√	√		
IMP and donepezil[l]		√	√	√	√	√	

Visit	Baseline II[a]	Treatment Period				Completion/ Withdrawal[b]	Safety Follow-up[c]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day[d]/ End of Week	**0**	**28/ 4**	**56/ 8**	**84/ 12**	**140/ 20**	**196/ 28**	**224/ 32**
Visit Window[e] (days relative to nominal visit)		**± 7d**	**± 7d**	**± 7d**	**± 7d**	**± 7d**	**+ 7d**
Screening/Baseline Procedures and Assessments							
hydrochloride returned accountability tracked							
Recent and concomitant medication	√[j]	√	√	√	√	√	√
Dispense Patient Identification card	√						
Patient Identification card returned						√[m]	
Informed Consent Provided [open-label treatment period with memantine (substudy)]					√[n]		

a. For the purposes of clarity, the Baseline Visit is called Baseline II Visit and this visit is the same as Visit 7 (Completion Visit) in the lead-in study.
b. This visit should take place as soon as possible after the patient withdraws from the study.
c. Patients who complete the study and do not enter into the open-label treatment period with memantine (sub-study) will have a Safety Follow-up Visit which is at least 4 weeks (+ up to 7 days) after the last dose of IMP. Patients withdrawn will likewise be followed-up 4 weeks (+ up to 7 days) after withdrawal except for those who withdraw their consent. Patients who withdraw their consent should still have a safety follow-up, but the visit must only be recorded in the medical records.
d. All assessments can be completed over a maximum of two consecutive days, in this case the first day should be considered as the visit day of the study. Note: If a visit takes place over two consecutive days the IMP should be dispensed on the second day, after all assessments have been performed. For visits other than the Baseline II visit, the visit window must allow for the previously dispensed IMP to last for both visit days.
e. If the date of a patient visit does not conform to the study plan, subsequent visits should be planned to maintain the visit schedule relative to Baseline II. Number of days between 2 visits must not exceed the number of days for which IMP is provided in the wallet cards.
f. Lead-in study screening visit (Visit 1) data transferred.
g. Assessments and procedures conducted at Visit 7 (Completion Visit) of the lead-in study will be transferred and will not be repeated at the Baseline II Visit of this extension study.
h. During evaluation the patient should be compared to Baseline I assessment of the lead-in study.
i. Data will be transferred from Visit 7 (Completion Visit) of the lead-in study or entered manually to the eCRF if the scale has been administered for the first time at Visit 1 of the extension study.
j. On-going adverse events and Concomitant Medications at Visit 7 (Completion Visit) from the lead-in study are to be transferred to the eCRF.
k. Only for adverse events on-going at Completion/Withdrawal Visit and new SAEs.
l. As base treatment, donepezil hydrochloride 10 mg/day will be dispensed as wallet cards.
m. *Patient Identification Card* should only be returned after the last dose of IMP has been taken, that is at the end of the treatment period.

n. For patients who may be eligible to participate in the open-label treatment period with memantine (sub-study), it is suggested that the *Informed Consent Form* is provided.

Study Procedures and Assessments [open-label treatment with memantine (sub-study)]

Visit	Baseline III[a]	Treatment Period			Completion/ Withdrawal[b]	Safety Follow-up[c]
Visit Number	**6**	**8[j]**	**9**	**10**	**11**	**12**
Day/[d]	**0**	**224/**	**252/**	**280/**	**364/**	**392/**
End of Week		**32**	**36**	**40**	**52**	**56**
Visit Window[e] (days relative to nominal visit)		**± 7d**	**±7d**	**± 7d**	**±7d**	**+ 7d**
Screening/Baseline Procedures and Assessments						
Signed informed consent	√					
Demographics, height	√					
Medical history	√					
Inclusion/exclusion criteria	√					
Efficacy Assessments						
MMSE	√[f]				√	
Pharmacoeconomic Assessments						
Patient's current living accommodation (question extracted from the RUD-Lite)	√[f]			√	√	
Dependence scale	√[f]			√	√	
Pharmacokinetic Assessments						
Blood sampling for idalopirdine and memantine	√	√	√	√	√	
Safety Assessments						
Adverse events	√[f]	√	√	√	√	√[g]
Blood and urine sampling for clinical safety laboratory tests	√[f]	√	√	√	√	
Vital signs, weight, ECGs	√[f]	√	√	√	√	
C-SSRS	√[f]	√	√	√	√	
Examinations (physical, neurological)	√[f]			√	√	
Other Study Procedures						
IMP and donepezil hydrochloride dispensed. Memantine prescribed[h]	√	√	√	√		
IMP, memantine and donepezil hydrochloride returned and accountability tracked[h]		√	√	√	√	
Recent and concomitant medication	√[f]	√	√	√	√	
Dispense Patient Identification card	√					
Patient Identification card returned				√[i]		

a. The Baseline Visit for this study (Baseline III) is the same visit as Visit 6 (end of Week 28) for patients who complete the open-label treatment period.
b. This visit should take place as soon as possible after the patient withdraws from the study.
c. Patients who complete the study will have a Safety Follow-up Visit which is at least 4 weeks (+ up to 7 days) after the last dose of IMP. Patients withdrawn will likewise be followed-up 4 weeks (+ up to 7 days) after withdrawal except for those who withdraw their consent. Patients who withdraw their consent should still have a safety follow-up, but the visit must only be recorded in the medical records.
d. All assessments can be completed over a maximum of two consecutive days, in this case the first day should be considered as the visit day of the study. Note: If a visit takes place over two consecutive days the IMP should be dispensed on the second day, after all assessments have been performed. For visits other than the Baseline Visit of this study, the visit window must allow for the previously dispensed IMP to last for both visit days.
e. If the date of a patient visit does not conform to the study plan, subsequent visits should be planned to maintain the visit schedule relative to Baseline III of this study. Number of days between 2 visits must not exceed the number of days for which IMP is provided in the wallet cards.
f. Assessments and procedures are the same as Visit 6 in the open-label treatment period.
g. Only for adverse events on-going at Completion/Withdrawal of this study and new SAEs.
h. Donepezil hydrochloride 10 mg/day will be dispensed as wallet cards. Memantine (titration doses plus patient's individualised maintenance dose) will be prescribed by the investigator or another medically-qualified person and the investigator should make sure that an adequate supply of memantine is prescribed to last between two visits (including visit windows). In addition to the return of IMP and donepezil hydrochloride, patient will be asked to bring used and unused memantine in original packaging to the visit for accountability purposes.
i. *Patient Identification Card* should only be returned after the last dose of IMP has been taken, that is at the end of the treatment period.
j. All patients entering the open-label treatment period with memantine (sub-study) will perform Visit 8 right after Visit 6 [Visit 7 is the Safety Follow-up visit only for patients who do not continue into the open-label treatment period with memantine (sub-study)].

Appendix III
SAS® Code

SAS® Code

The SAS code for the MMRM-analysis (for each lead-in study) will be:

```
%**MMSTR=MMSE stratum;
proc mixed noclprint data=ADAS ic method=REML;
    class usubjid country analysis_week armcd MMSSTR;
    model ADASTOT_DL = ADASTOT_BL MMSSTR country armcd analysis_week
        armcd*analysis_week MMSSTR*analysis_week ADASTOT_BL*analysis_week
        /s DDFM=KR;
    repeated analysis_week/subject=usubjid type=un;
run;
```

Appendix IV
PCS Criteria

PCS Criteria

Table 1 PCS Criteria for Clinical Safety Laboratory Tests

CDISC term	Test (units)	PCS Low	PCS High
Liver			
AST	S-aspartate aminotransferase (IU/L)		≥ 3 × ULN
ALT	S-alanine aminotransferase (IU/L)		≥ 3 × ULN
BILI	S-bilirubin (µmol/L)		≥ 34
BILDIR	S-direct bilirubin (µmol/L)		≥ 12
ALP	S-alkaline phosphatase (IU/L)		≥ 3 × ULN
GGT	S-gamma glutamyl transferase (IU/L)		≥ 200
Kidney			
CREAT	S-creatinine (µmol/L)		≥ 1.5 × ULN
BUN	B-urea nitrogen (mmol/L)		≥ 11
Electrolytes			
SODIUM	S-sodium (mmol/L)	≤ 125	≥ 155
K	S-potassium (mmol/L)	≤ 3.0	≥ 6.0
CA	S-calcium (mmol/L)	≤ 1.8	≥ 3.0
BICARB	S-bicarbonate (mmol/L)	≤ 12	≥ 38
Endocrine/Metabolic			
GLUC	Serum glucose (mmol/L)	≤ 3.9	≥ 11.1
GLUC	Serum glucose, fasting (mmol/L)	≤ 3.5	≥ 7.0
TSH	S-thyrotropin (mIU/L)	≤ 0.3	≥ 5.5
ALB	Albumin (g/L)	≤ 27	
Lipids			
CHOL	S-cholesterol (mmol/L)		≥ 7.8
CHOL	S-Cholesterol, fasting (mmol/L)		≥ 6.2
TRIG	Triglycerides (mmol/L)		≥ 5.65
TRIG	Triglycerides, fasting (mmol/L)		≥ 4.2
Haematology/Coagulation			
INR	P-INR (Prothrombin ratio)		≥ 2.0
PLAT	B-thrombocytes platelet count (×10E9/L)	≤ 75	≥ 600
HGB	B-haemoglobin (g/dL)	≤ 9.5 (women) ≤ 11.5 (men)	≥ 16.5 (women) ≥ 18.5 (men)
RBC	B-erythrocytes (×10E12/L)	≤ 3.5 (women) ≤ 3.8 (men)	≥ 6.0 (women) ≥ 7.0 (men)
WBC	B-Leukocytes (×10E9/L)	≤ 2.8	≥ 16
NEUTLE	B-Neutrophils/leukocytes (%)	≤ 20	≥ 85
EOSLE	B-eosinophils/leukocytes (%)		≥ 10

CDISC term	Test (units)	PCS Low	PCS High
BASOLE	B-basophils/leukocytes (%)		≥ 10
LYMLE	B-Lymphocytes/leukocytes (%)	≤ 10	≥ 75
MONOLE	B-Monocytes /leukocytes (%)		≥ 15
Infection			
CRP	S-C-reactive protein (mg/L)		≥ 25
Urine			
GLUC	U-Glucose		Increase≥2
KETONES	U-Ketones		Increase≥2
OCCBLD	U-Occult Blood		Increase≥2

Table 2 PCS Criteria for Vital Signs and Weight

CDISC term	Variable (units)	PCS Criterion Low	PCS Criterion High
WEIGHT	Weight (kg)	Decrease ≥ 7%	Increase ≥ 7%
BMI	Body mass index (kg/m2)	Decrease ≥ 7%	Increase ≥ 7%
DIABP	Supine diastolic blood pressure (mmHg)	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
SYSBP	Supine systolic blood pressure (mmHg)	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
PULSE	Pulse rate supine/sitting/unknown (bpm)	≤ 50 and decrease ≥ 15	≥ 120 and increase ≥ 15

Table 3 PCS Criteria for ECG Parameters

CDISC term	Parameter (units)	PCS Criterion Low	PCS Criterion High
Absolute Time Interval			
PRMEAN	PR interval (msec)		≥ 260
QRSDUR	QRS interval (msec)		≥ 150
QTMEAN	QT interval (msec)		≥ 500
Derived Time Interval			
QTcB	QTcB interval (msec)	< 300	> 500 or increase > 60
QTcF	QTcF interval (msec)	< 300	> 500 or increase > 60
HRMEAN	ECG Mean heart rate (beats/min)	≤ 50 and decrease ≥ 15	≥ 120 and increase ≥ 15