Electronic Signature Page

Full Title
Randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil; study 1

Short Title
14861A - Statistical Analysis Plan Amendment - 1

Study Number 14861A

The following persons have electronically signed this document

Server Date and Time	Signed by
09-Sep-2016 07:06:57	AKTH Anna Karina Trap Huusom
Reason for Signature	Management Approval

09-Sep-2016 07:10:00	ANBL Anna Bladström
Reason for Signature	Biostatistic Approval

09-Sep-2016 10:01:26	NEBO Neli Boneva
Reason for Signature	Clinical Approval

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Statistical Analysis Plan – Amendment 1

Randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil; study 1

Idalopirdine

Study No.:	14861A
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Biostatistician:	Anna Bladström, Biostatistics
SAP date:	29 April 2016
SAP Amendment date:	5 September 2016

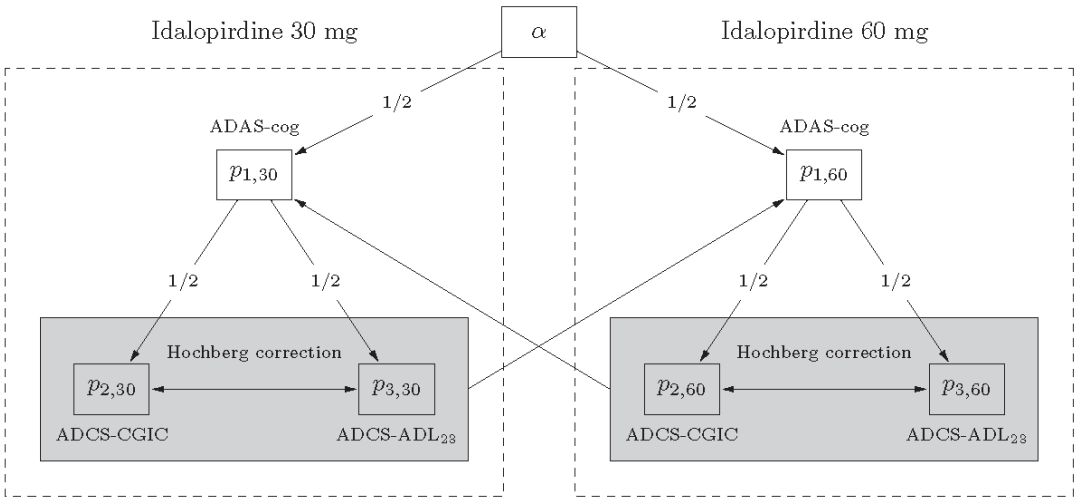
1 Rationale for this SAP Amendment

This amendment contains a detailed description of how to compute adjusted p-values in the testing hierarchy described in the SAP. It does not represent any changes in planned analyses or methodology, but is an elaboration of the methods used in connection with the described testing strategy. The reason for this amendment is that the described methodology is non-trivial and is not considered standard.

2 Computing adjusted p-values

The testing strategy for 14861A is displayed in Panel 1 using the graphical approach of Bretz et al.[1] The weights on the arrows indicate the proportion of α that is transferred when the test is significant. If no weights are given the full available significance level is transferred. An adjusted p-value at a given location in Panel 1 is the minimal significance level α that, respecting the test hierarchy, would make the corresponding raw p-value significant. Computing adjusted p-values is not straightforward because of the complexity of the testing graph and the two Hochberg corrections.[2] The Hochberg corrections are valid because of the positive dependence of the corresponding test statistics, and improve conventional Bonferroni-type corrections by allowing for simultaneous testing of the two hypotheses at the full available significance level.

Panel 1 Testing strategy



In the following, we will outline a sequential procedure for computing the adjusted p-values in two steps.

Step 1: Because of symmetry, we begin by computing the adjusted p-values within each of the two dose groups without any transmission of α between doses. For the 60 mg dose the first-step adjusted p-values are given by

$$\tilde{p}_{1,60} = 2p_{1,60}$$

$$\tilde{p}_{2,60} = \max(\tilde{p}_{1,60}, \min(4p_{2,60}, \max(2p_{2,60}, 2p_{3,60})))$$

$$\tilde{p}_{3,60} = \max(\tilde{p}_{1,60}, \min(4p_{3,60}, \max(2p_{2,60}, 2p_{3,60})))$$

and similarly for the 30 mg dose. The rationale for the structure of the adjusted p-values for the key secondary endpoints is as follows. The outer maximum arises because the testing hierarchy dictates that the corrected p-values cannot be less than the adjusted p-value for the primary endpoint (α can only be transferred once the hypothesis is rejected). The adjusted p-value is the least α level that makes the observed p-value significant, which can either happen by means of the Bonferroni corrected level (quarter α level) or in terms of the Hochberg correction (which includes simultaneous testing of both p-values at half α level).

Step 2: Once the adjusted p-values have been computed in step 1, we need to allow the overall most significant dose to transfer its α level to the less significant dose. The most significant dose is the dose for which the maximum of the first-step corrected p-values for the key secondary endpoints is smallest, since we can only transfer α when both hypotheses are rejected. The first-step adjusted p-values for this dose will not change further. In the following, we will assume that the 60 mg dose had the lowest combined p-value

$$\tilde{p}_{60} = \max(\tilde{p}_{2,60}, \tilde{p}_{3,60}).$$

The reversed situation is handled using the exact same procedure as described below.

To compute the final adjusted p-values for the 30 mg dose, we should calculate

$$\tilde{p}_{1,30} = \min(2\,p_{1,30}, \max(p_{1,30}, \tilde{p}_{60}))$$

$$\tilde{p}_{2,30} = \max(\tilde{p}_{1,30}, \min(4p_{2,30}, \max(2p_{2,30}, 2p_{3,30}), \max(\tilde{p}_{60}, \min(2p_{2,30}, \max(p_{2,30}, p_{3,30})))))$$

$$\tilde{p}_{3,30} = \max(\tilde{p}_{1,30}, \min(4p_{3,30}, \max(2p_{2,30}, 2p_{3,30}), \max(\tilde{p}_{60}, \min(2p_{3,30}, \max(p_{2,30}, p_{3,30})))))$$

The rationale for these adjustments is as follows. The primary endpoint can either be tested on

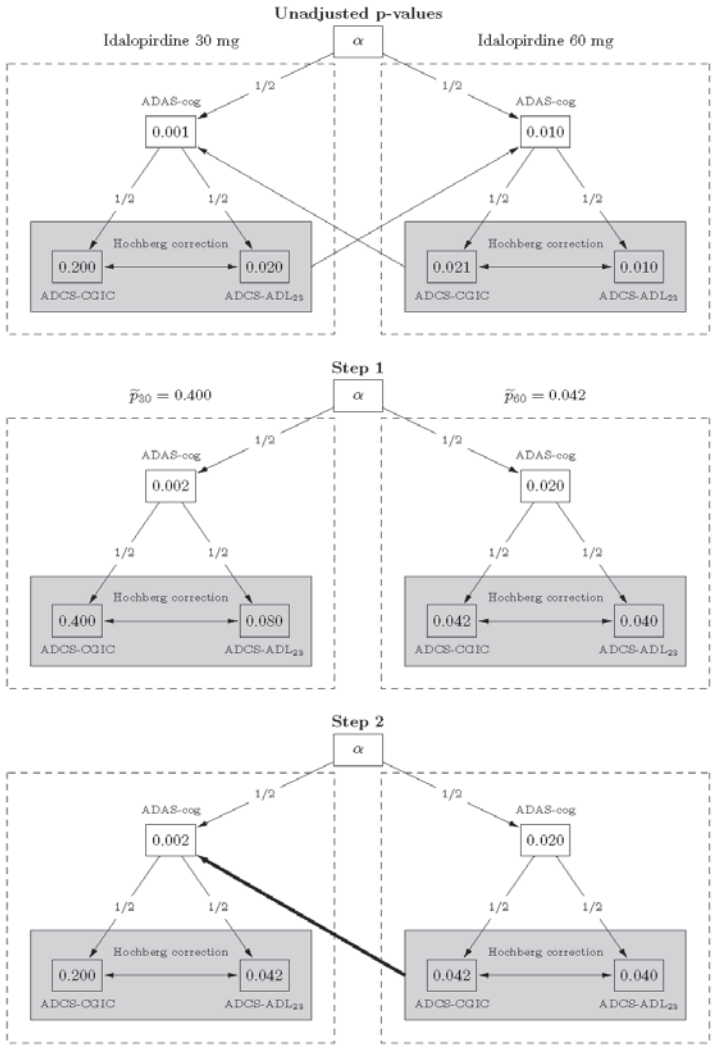
half the α level as before, or it can be tested on full level $\alpha \geq \tilde{p}_{60}$, corresponding to the least significance level that makes all the 60 mg tests significant. The adjusted p-value is the least of these two cases. For the key secondary endpoints, again the adjusted p-values cannot be less than the adjusted p-value for the primary endpoint (outer maximum). To compute the adjusted p-values we must take the minimum over two possible scenarios:

- Bonferroni or Hochberg correction on quarter and simultaneous half α level without transferred α (same as in first step), or
- Bonferroni or Hochberg correction on half and simultaneous full level $\alpha \geq \tilde{p}_{60}$ (last term in minimum).

The overall adjusted p-value for a dose is the least α that would make the primary and one of the key secondary endpoints significant, in other words, the minimum of the adjusted p-values for the key secondary endpoints within the dose.

2.1 Example (made-up data)

The procedure for correcting adjusted p-values is illustrated in the figure below on a set of made up raw p-values.



In this setup, the overall adjusted p-value for the 60 mg dose is 0.040 and the overall adjusted p-value for the 30 mg dose is 0.042.

2.2 References

1. Bretz, F., Maurer, W., Brannath, W., and Posch, M. "A graphical approach to sequentially rejective multiple test procedures." *Statistics in Medicine* 28.4 (2009): 586-604.

2. Benjamini, Y. and Yekutieli D. "The control of the false discovery rate in multiple testing under dependency." *Annals of Statistics* (2001): 1165-1188.

Statistical Analysis Plan – Amendment 1
Authentication and Authorisation

Study title:	Randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil; study 1
Study No.:	14861A
SAP Amendment date:	5 September 2016

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

Authentication

Biostatistician:	Anna Bladström
Clinical research scientist:	Neli Boneva, CRD Neurology

Authorisation

Head of Biostatistics:	Anna Karina Trap Huusom

Electronic Signature Page

Full Title
Randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil; study 1

Short Title
14861A - Statistical Analysis Plan

Study Number 14861A

The following persons have electronically signed this document

Server Date and Time	Signed by
29-Apr-2016 17:05:03	ANBL Anna Bladström
Reason for Signature	Author

01-May-2016 11:00:16	AKTH Anna Karina Trap Huusom
Reason for Signature	Management Approval

02-May-2016 09:42:24	NEBO Neli Boneva
Reason for Signature	Clinical Approval

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Statistical Analysis Plan

Randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil; study 1

Idalopirdine

Study No.:	14861A
Sponsor:	H. Lundbeck A/S (Lundbeck)
	2500 Valby (Copenhagen), Denmark
Biostatistician:	Anna Bladström, Biostatistics
SAP date:	29 April 2016

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

aCRF	Annotated case report form
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
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ALP	alkaline phosphatase
APRS	all-patients-randomised set
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	Area Under Curve
BILI	Total serum bilirubin
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CYP	cytochrome P450 isoenzyme
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
FAS	full-analysis set
FDA	United States Food and Drug Administration
GGT	gamma glutamyl transferase
HR	heart rate
IMP	investigational medicinal product
INR	international normalised ratio of prothrombin time
MAR	missing at random
MCMC	markov chain monte carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	mixed model for repeated measurements
MMSE	Mini mental state exam
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

NPI	Neuropsychiatric Inventory
OC	observed cases
PBO	placebo
PCS	potentially clinically significant
PMM	Pattern mixture model
PR	specific ECG interval describing atrioventricular conduction
PYE	patient years of exposure
QRS	specific ECG interval describing ventricular depolarisation
QT	specific ECG interval describing ventricular depolarisation/repolarisation
QTcB	heart-rate corrected QT interval using Bazett's correction formula
QTcF	heart-rate corrected QT interval using Fridericia's correction formula
REML	restricted maximum likelihood
RUD Lite	Resource Utilisation in Dementia Lite
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	statistical software package from the SAS® Institute
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 Objectives

1.1 Primary Objective

To establish efficacy of idalopirdine as adjunctive therapy to donepezil for symptomatic treatment of patients with mild-moderate Alzheimer's disease.

1.2 Secondary Objective

To investigate the effect of idalopirdine as adjunctive therapy to donepezil on neuropsychiatric symptoms in patients with mild-moderate Alzheimer's disease.

1.3 Other Objective

To explore population pharmacokinetics (PK)/pharmacodynamics (PD).

1.4 Safety Objective

To evaluate the safety and tolerability of idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate Alzheimer's disease.

2 Study Design

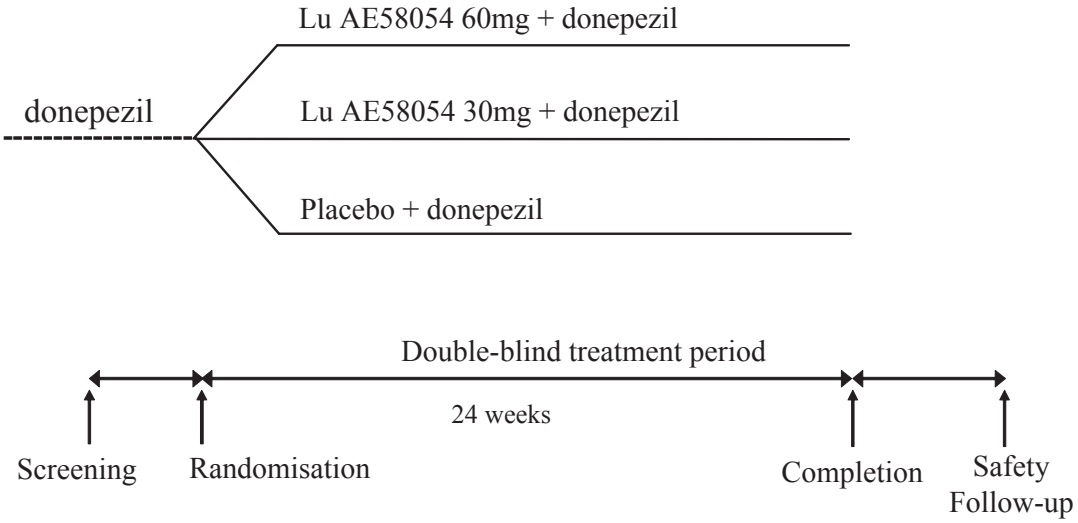
This is an interventional multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of idalopirdine as adjunctive treatment to donepezil in patients with mild-moderate Alzheimer's disease (AD).

The total study duration per patient from baseline to the end of follow-up will be approximately 28 weeks. The patients will be treated with the double blind IMP as add on therapy to the base treatment donepezil 10 mg. The study will include the following periods:

- 2-week screening period
- 24-week double-blind (idalopirdine 30 or 60 mg/day or placebo) *treatment period* (Visit 2 to Visit 7) as add-on to donepezil 10 mg/day
- 4-week safety follow-up period

The study design is presented in Panel 1 and the scheduled assessments are summarised in Appendix II (study flow chart).

Panel 1 Study Design



Patients were randomised via a centralised randomisation system (Interactive Voice Response System [IVRS]). Randomisation was stratified by Mini Mental State Exam (MMSE) stratum (<19, ≥19). Randomisation was restricted such that at most 50% of the patients are in the MMSE 19-22 (mild) stratum.

The group of patients who withdrew from the *treatment period* will be described as *withdrawn from treatment*. The complementary group will be described as *completed treatment*.

The study includes a follow-up of withdrawn patients, except for those who withdraw their consent, 4 weeks after the Withdrawal Visit (Withdrawal Follow-up Visit), and at the projected time of the primary endpoint (Drop-out Retrieval Visit) if the patient withdraw before week 18. The Withdrawal follow-up Visit and Drop-out Retrieval Visit include collection of data to address the primary and key secondary endpoints. The efficacy data collected after withdrawal from treatment will be designated *follow-up efficacy data* (that is, data collected at the Withdrawal Follow-up Visit, and at the Drop-out Retrieval Visit). The *follow-up efficacy data* will only be used for sensitivity analyses.

3 Endpoints

3.1 Primary Endpoint

The primary endpoint addresses the primary objective of the study.

- Cognition:
  - Change from baseline to Week 24 in Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) total score

3.2 Key Secondary Endpoints

The key secondary endpoints address the primary objective of the study.

- Global impression:
  - Alzheimer's disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) score at Week 24
- Function:
  - Change from baseline to Week 24 in Alzheimer's disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL_{23}) total score

3.3 Secondary Endpoints

The secondary endpoints address the secondary objective, are supportive of the primary objective or address other objectives of the study.

- Endpoints addressing the secondary objective:
  - Change from baseline to Week 24 in Neuropsychiatric Inventory (NPI) total score
  - Change from baseline in single NPI items at Week 24
  - Change from baseline to Week 24 in NPI single items in patients with an item score of at least 2 at baseline
  - Emergence of individual NPI items (score≥3) at Week 24. The analyses will be based on patients with an item score of <3 at baseline
  - Change from baseline in NPI caregiver distress total score at Week 24
- Endpoints that are supportive of the primary objective:
  - Clinical response at Week 24 (ADAS-cog change ≤ -4 and ADCS-ADL_{23} change ≥0 and ADCS-CGIC<=4)
  - Clinical response at Week 24 where response is defined using cut-offs of ≤-3, ≤-2 , ≤-1 for ADAS-cog change, ADCS-ADL_{23} change ≥0 and ADCS-CGIC<=4)
  - Clinical worsening at Week 24 (ADAS-cog change ≥4 and ADCS-ADL_{23} change <0 and ADCS-CGIC >4)
  - Change from baseline to Week 24 in Mini Mental State Examination (MMSE) total score
  - Change from baseline to Week 24 in EQ-5D utility score
  - Change from baseline to Week 24 in EQ-5D VAS
  - Area under curve (AUC) from baseline to week 24 for the changes from baseline in ADAS-Cog total score
  - AUC from baseline to week 24 for the changes from baseline in ADCS- ADL_{23} total score
  - AUC from baseline to week 24 for the ADCS-CGIC minus four (as ADCS-CGIC is an assessment of changes, i.e. no change in health state corresponds to a score of 0)
  - Change from Baseline to Week 24 in ADAS-Cog and ADCS- ADL_{23} composite score
  - AUC from baseline to week 24 for the changes from baseline in ADAS-Cog and ADCS- ADL_{23} composite score

  - Change from Baseline to Week 24 in Basic ADCS- ADL_{23}
  - Change from Baseline to Week 24 in Instrumental ADCS- ADL_{23}
- Endpoints addressing other objectives:
  - Plasma concentrations of idalopirdine and donepezil

3.4 Safety Endpoints

Endpoints addressing safety objectives:
- Adverse events
- Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, and ECG parameters
- Potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values
- C-SSRS

4 Analysis Sets

The classification will be based on IMP intake and post-baseline assessments of the primary efficacy variable (ADAS-Cog) in the *Treatment period*.

The sets of patients to be analysed are defined as follows:
- all-patients-randomised set (APRS) – all randomised patients
- *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of IMP
- full-analysis set (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the primary efficacy variable

The patients and data will be classified into the analysis sets according to the definitions above after the study database has been released but before the blind has been broken.

If a patient received the incorrect IMP (IMP not randomised to), all analyses will be based on the randomised treatment but information about the actual treatment and the start-and stop date(s) when incorrect IMP was received will be included as a footnote in output where relevant. Additional listing will also be prepared if needed.

5 Descriptive Statistics

Unless otherwise specified, summary statistics (n, and at a minimum arithmetic mean, standard deviation [SD], median, minimum and maximum) will be presented for continuous variables, and counts and percentages will be presented for categorical variables.

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

6 Patient Disposition

6.1 Summary of Patient Disposition

Patient disposition will be summarised by treatment group and include the number of patients in each analysis set defined in chapter 4, and the number of patients in the APTS who completed or withdrew from treatment.

All analyses will be repeated by MMSE stratum.

6.2 Withdrawal

The number of patients who withdrew from treatment will be summarised by treatment group and primary reason for withdrawal as well as by treatment group and all reasons for withdrawal. Reasons for withdrawal collected in the study were adverse events, protocol violation, withdrawal of consent, lost to follow-up, and other reasons.

Patients who withdrew from treatment will be listed and the listing will include the number of days in the study until withdrawal from treatment, exposure to IMP (see definition in chapter 9), the primary reason for withdrawal, and all reasons for withdrawal.

The cumulative number of withdrawals from treatment at visit weeks 4, 8, 12, 18, and 24 for each primary reason of withdrawal will be presented by treatment group. The Withdrawal Visit will be assigned to the closest scheduled visit not attended in the *Treatment period*.

Kaplan-Meier plots of time to withdrawal from treatment will be presented by treatment group. The time will be calculated from the date of first dose of IMP to the date of completion or withdrawal from treatment. Patients who completed treatment will be regarded as censored

Nelson-Aalen cause specific cumulative hazard plots of time to withdrawal from treatment will be generated for each primary reason. The time will be calculated from the date of first dose of IMP to the date of completion or withdrawal from treatment.

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

All analyses will be repeated by MMSE stratum.

7 Demographics and Other Baseline Characteristics

Demographics (age, age groups [<65, 65-74, 75-84 and ≥ 85], sex, ethnicity, and race), patient characteristics (weight, height, BMI, smoking, other nicotine use, alcohol use, years of education, marital status, and ApoE4 positive [ApoE genotype E2/E4, E3/E4, or E4/E4]), Alzheimer's disease and family history of AD (MMSE stratum, MMSE total score at baseline, years since diagnosis [see paragraph 18.4.3], previous treatment with memantine, previous treatment with Acetylcholinesterase inhibitor (AChEI) other than Donepezil, participation in

randomized Alzheimer´s disease trials, duration of donepezil treatment [see paragraph 18.4.2], and number of first degree relatives with a diagnosis in Alzheimer's disease), and efficacy variables at baseline will be summarised by treatment group.

The medical, neurological, and psychiatric histories, as well as concurrent medical, neurological, or psychiatric disorders will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1 or later, and summarised by treatment group. A medical, neurological, or psychiatric history is a disorder that ended prior to the Screening Visit. A concurrent medical, neurological, or psychiatric disorder is a disorder that is ongoing at the Screening Visit.

Demographics and other baseline characteristics will be summarised based on the APTS.

All analyses will be repeated by MMSE stratum.

8 Recent and Concomitant Medication

Recent and concomitant medication will be coded using the WHO Drug Dictionary (WHO-DDE), Version 12.1, or later.

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

- medication discontinued prior to first dose of IMP
- concomitant medication continued after first dose of IMP
- concomitant medication started at or after first dose of IMP and at or before the completion/withdrawal Visit
- Treatment for Alzheimer’s disease (identified by ATC code N06D) started after the Withdrawal Visit in withdrawn patients

For details about handling of missing dates, see paragraphs 18.4.1 (IMP start date), and 18.4.5 (medication start, and stop dates).

The tables will be based on the APTS.

9 Exposure and Compliance

Exposure to IMP will be defined as:

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

For handling of missing IMP start-or stop date, see paragraph 18.4.1.

Exposure to IMP will be summarised by treatment group using descriptive statistics, and include the patient years of exposure (PYE) to IMP. 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 will be categorised into day intervals (1 to 27, 28 to 55, 56 to 83, 84 to 125, 126 to 167, and ≥168) and summarised by treatment group.

Exposure to donepezil will be defined and summarised in the corresponding way as exposure to IMP.

Non-compliance days will be defined as days on which no IMP has been taken.

Compliance with IMP (%) in the *treatment period* will be defined as the compliance for the interval between the date of Randomisation+1 (the first IMP should be taken the day after the randomisation) and the Completion/Withdrawal Visit:

{date of Completion/Withdrawal Visit – date of Randomisation – total number of days of non-compliance } / {date of Completion/Withdrawal Visit – date of Randomisation} × 100%

Compliance with IMP (%) will also be defined for intervals between consecutive scheduled visits in the *treatment period*. The first visit interval will be the interval between date of randomisation +1 and Date of Visit 3, and thereafter intervals between $Visit_i$ and $Visit_{i+1}$, i=3,4, 5, and 6.

For details on data handling issues, see paragraphs 18.4.4 and 18.5.

Compliance with IMP will be summarised by treatment group, both by visit interval and for the entire *treatment period*.

Compliance with donepezil will be defined and summarised in the corresponding way as compliance with IMP.

Exposure and compliance will be summarised based on the APTS.

10 Efficacy

10.1 General Efficacy Analysis Methodology

Primary, key-secondary, and secondary endpoints and the type (continuous, categorical, or binary) are summarised in Panel 2.

Panel 2 Endpoints

Endpoint	Type
Primary	
Change from baseline to Week 24 in ADAS-cog total score	1
Key-secondary	
ADCS-CGIC score at Week 24 (assessment of patient change compared to patient's condition at the baseline Visit)	1,2
Change from baseline to Week 24 in ADCS-ADL_{23} total score	1
Secondary	
Change from baseline to Week 24 in NPI total score	1
Change from baseline in single NPI items at Week 24 (12 endpoints)	1
Change from baseline to Week 24 in NPI single items in patients with an item score of at least 2 at baseline (12 endpoints)	1
Emergence of individual NPI items (score≥3). The analyses will be based on patients with an item score of <3 at baseline (12 endpoints)	3
Change from baseline in NPI caregiver distress total score	1
Clinical response at Week 24 (ADAS-cog change ≤ -4 and ADCS-ADL_{23} change ≥0 and ADCS-CGIC<=4)	3
Clinical response at Week 24 where response is defined using cut-offs of ≤-3, ≤-2 , ≤-1 for ADAS-cog change, ADCS-ADL_{23} change ≥0 and ADCS-CGIC<=4 (three endpoints)	3
Clinical worsening at Week 24 (ADAS-cog change ≥4 and ADCS-ADL23 change <0 and ADCS-CGIC >4)	3
Change from baseline to Week 24 in MMSE total score	1
Change from baseline to Week 24 in EQ-5D utility score	1
Change from baseline to Week 24 in EQ-5D VAS	1
Area under curve (AUC) from baseline to week 24 for the changes from baseline in ADAS-Cog total score	1
AUC from baseline to week 24 for the changes from baseline in ADCS-ADL_{23} total score	1
AUC from baseline to week 24 for the ADCS-CGIC scores minus four (as ADCS-CGIC is an assessment of changes, i.e. no change in health state corresponds to a score of 0)	1
Change from baseline to Week 24 in ADAS-Cog and ADCS- ADL_{23} composite score	1
AUC from baseline to week 24 for the changes from baseline in ADAS-Cog and ADCS-ADL_{23} composite score	1
Change from baseline to Week 24 in Basic ADCS-ADL_{23}	1
Change from baseline to Week 24 in Instrumental ADCS-ADL_{23}	1
Plasma concentrations of idalopirdine and donepezil	1

1 = continuous; 2 = categorical; 3 = binary

For details about data handling issues in the derivation of variables and assigning data to visits (weeks), see paragraph 18.2 and 18.3.1.

Unless otherwise specified, all the efficacy analyses will be based on the FAS.

All the tables and graphs will be presented by treatment group.

The *follow-up efficacy data* will only be used for sensitivity analyses (see last section in chapter 2).

Absolute values and change from baseline values (if defined) for the efficacy variables (MMSE total score, ADAS-Cog total score, ADCS-ADL_{23}total score, Basic ADCS-ADL_{23}, Intrumental ADCS-ADL_{23}, ADCS-CGIC, NPI total score, NPI items, and NPI caregiver distress total score) will be summarised by visit week and treatment group, using available observations in the *treatment period*. ADCS-CGIC will be summarised both as a continous and as a categorical variable. Descriptive statistics for efficacy variables will be repeated by MMSE stratum.

Countries and sites where not all treatment groups are represented in the FAS will be grouped according to the specification in paragraph 18.6, and the grouped variable will be used in the efficacy analyses where country/site is included.

All the p-values will be based on two-sided tests; and all confidence intervals (CIs) will be two-sided symmetric 95% CIs.

10.2 Analysis Methodology for the Primary Endpoint

10.2.1 Analysis of the Primary Endpoint

Change from baseline in ADAS-Cog total score will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The model will include treatment (placebo, idalopirdine 30 mg, and idalopirdine 60 mg), country, MMSE stratum (<19, ≥19), and week (4, 12, and 24) as fixed categorical effects, baseline ADAS-cog total score as a continuous covariate, treatment-by-week interaction, MMSE stratum-by-week interaction, and baseline score-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The analysis will be based on the missing-at-random (MAR) assumption and performed using all available observations (observed cases [OC] data) in the *treatment period*. The SAS code for the analysis included in Appendix III.

If, this model fails to converge, the following (co)variance structures will be tested: first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The (co)variance structure converging to the best fit, as determined by Akaike's information criterion, will then be used as the primary analysis.

The mean differences between each dose of idalopirdine (30 mg and 60 mg) and placebo will be estimated based on the least squares means for the treatment-by-visit interaction in the MMRM-model. The estimates will be presented with nominal p-values and 95% CIs. The primary comparisons will be the contrasts between each dose of idalopirdine and placebo at Week 24. Details of the statistical testing for the primary endpoint are provided in paragraph 10.4.

MMRM analysis pooling the 30 mg and 60 mg doses into one arm and testing the effect of 30 mg and 60 mg pooled, versus placebo, will be performed on an exploratory basis.

10.2.2 Rationale for Selected Analysis Method for the Primary Endpoint

The MMRM analysis uses all available data measured repeatedly over time and allows for evaluation of the treatment-by-time interaction. The MMRM analysis provides an unbiased estimate of the treatment effect under the assumption that missing data are MAR.

Published data support the robustness of the MMRM analysis regarding protection against type I error and against bias, also in situations with a non-negligible proportion of missing data. Using extensive simulations, it has been demonstrated that the type I error is only affected to a limited extent and that the bias is small under the assumption that 1/3 of the missing data are missing-not-at-random, even when there is a severe imbalance between the treatment groups in the proportion of withdrawals.[1]

10.2.3 Subgroup Analyses and Model Assumptions for Analysis of the Primary Endpoint

A plot with mean values-by-week will be presented, grouped by withdrawal pattern (week of last available value). At or before last available week, the mean values will be the mean of observed (unadjusted) values. The mean values after last available week will be based on values predicted from the MMRM model in paragraph 10.2.1. Solid lines will indicate observed pattern, and dotted lines will indicate predicted pattern. The plot will include information about the number of patients for each withdrawal pattern. The plot will also be generated separately for each primary reason for withdrawal.

Subgroups of special interest are (ranked in the listed order):

- MMSE stratum
- Apathy (Yes/No), where apathy is defined as NPI item apathy score>0 at baseline
- Age groups age<85 and age≥85

The assumption of equal treatment effect for the MMSE stratum will be investigated. Analysis will be performed for each stratum separately, using the same methodology as that described for the primary analysis (see paragraph 10.2.1) excluding MMSE stratum and MMSE stratum-by-visit interaction from the model.

The assumption of equal treatment effect for the MMSE stratum will also be investigated by adding the three way interaction MMSE stratum-by-treatment-by-week to the model in the primary analysis (see paragraph 10.2.1). The treatment effect for each dose of idalopirdine compared to placebo in each stratum will be estimated by least square means for the contrast MMSE stratum-by-treatment-by-week. The primary comparisons will be the contrasts between each dose of idalopirdine and placebo in each stratum at Week 24. The p-value for the test of equal treatment effect across the MMSE stratum for each dose idalopirdine compared to placebo at week 24 will be presented.

The subgroup analysis of patients with or without apathy at baseline is to test if apathy may serve as a phenotypic marker for a cohort of patients with higher level of response. The analysis will be conducted as described for MMSE stratum.

Consistency of effect across age groups will be evaluated with the corresponding analyses as for MMSE stratum.

10.2.4 Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses will be performed to evaluate how different assumptions affect the estimates of the treatment effect.

The total number of patients with a value of the primary endpoint, and the number of patients of those who had a value included in the primary analysis, or a value collected in the withdrawal follow-up will be summarised.

Individual subject-by-time (actual time) plots of the primary variable by primary reason for withdrawal or completion will be presented, including follow-up efficacy data. Data captured in the *treatment period* will be indicated with solid lines, and data captured in the withdrawal follow-up period will be indicated with dashed lines. Time of first and last IMP intake will be marked in the plot.

The same MMRM analysis as that described for the primary endpoint in paragraph 10.2.1 including *follow-up efficacy data* for patients withdrawn from treatment will be done as a sensitivity analysis.

An analysis using a pattern-mixture model (PMM) will be performed, in which monotone missing values in patients withdrawn from treatment will be imputed using multiple imputation (MI) based on the placebo group.[2,3] The analysis will be based on the set of patients that are included in the primary analysis. The PMM assumes that the distribution for patients who withdraw from treatment is equal to the conditional distribution for the placebo group with the corresponding past. This is the basis for the multiple imputation of the monotone missing values in all treatment groups. The PMM model will include country, MMSE stratum, baseline ADAS-cog total score, and change from baseline in ADAS-Cog total score at week 4, 12, and 24. To prepare data for the PMM, a dataset with only monotone missing values will be created, imputing non-monotone missing values by MI based on a markov chain monte carlo (MCMC) model. The assumption in the MCMC model is that non-monotone missing values are missing at random. The MCMC analysis will be performed by treatment group and MMSE stratum and the model will include baseline ADAS-Cog total score, and change from baseline in ADAS-Cog total score at week 4, 12, and 24. In total, 200 simulations will be performed using random seeds 17345 (MCMC model) and 4387410 (PMM).

The 200 datasets will be analysed using the MMRM model specified in paragraph 10.2.1. Monotone missing values in patients that are not withdrawn from treatment will be assumed to be MAR, and missing values imputed from the PMM in those patients will be re-set to missing before the MMRM-analysis. The estimated treatment effects and standard errors

across the 200 simulations will be combined to produce a unique point estimate and standard error, taking into account the uncertainty of the imputation.[4] This approach will generally provide a conservative estimate of the treatment effect since it both penalises high withdrawal rates as well as higher withdrawal rates on the experimental therapy. The SAS code for the analysis included in Appendix III.

A plot with mean values-by-week will be presented, grouped by withdrawal pattern (week of last available value). At or before last available week, the mean values will be the mean of observed (unadjusted) values. The mean values after last available week will be based on values imputed from the PMM (values for patients withdrawn from treatment) and values predicted from the MMRM model (values for patients not withdrawn from treatment). Solid lines will indicate observed pattern, and dotted lines will indicate imputed/predicted pattern. The plot will include information about the number of patients for each withdrawal pattern.

Modifications where only data missing due to adverse events (primary reason) are imputed using the same methodology (PMM) will also be performed (that is, data missing due to the other reasons for withdrawal [protocol violation, withdrawal of consent, and other reasons] will be assumed to be MAR).

An analysis with country replaced by site in the model described in paragraph 10.2.1 will be performed.

An analysis with MMSE total score at baseline as a continuous covariate, and MMSE total score at baseline-by-week interaction added to model described in paragraph 10.2.1 will be performed.

10.3 Analysis Methodology for the Key Secondary Endpoint

10.3.1 Analysis of the Key Secondary Endpoints

For the key secondary endpoints, ADCS-CGIC and ADCS-ADL_{23}, the same methodology as that described for the primary analysis (see paragraph 10.2.1) will be used. For ADCS-CGIC, the scores at each visit will be analysed as opposed to changes from baseline since the score itself is an assessment of change from baseline. The ADCS-CGIC score at baseline, which is a clinical status evaluation, will be included for covariate adjustment, however.

The testing strategy for the key secondary endpoints is described in paragraph 10.4.

10.3.2 Rationale for Selected Analysis Method for the Key Secondary Endpoints

The rational is the same as described for the primary endpoint, see paragraph 10.2.2.

10.3.3 Subgroup Analyses and Model Assumptions for Analysis of the Key Secondary Endpoints

Investigation of the robustness of the model assumptions and consistency of treatment effect across subgroups will be performed in the corresponding way as for the primary endpoint, see paragraph 10.2.3.

10.3.4 Sensitivity Analyses of the Key Secondary Endpoints

The corresponding sensitivity analyses as for the primary endpoint (see paragraph 10.2.4) will be applied for the key-secondary endpoints.

In addition, for ADCS-CGIC at week 24, a logistic regression model for ordinal response will be applied to explore sensitivity to the normal distribution assumption for this variable in the primary analysis. The model will include treatment as a factor and baseline score as a covariate. The possible responses are {1,2,3,4,5,6,7}. Because the extreme categories are rare the responses will be grouped as {(1,2),3,4,5,(6,7)}. The analysis will be based on observed cases, using a logit link function to relate the underlying latent variable to the probability of observing a response less than or equal to a given ordered response.

Likelihood-ratio statistics and corresponding p-values for the dose effects at week 24 will be derived from the maximum likelihood estimates and standard errors of the regression parameters for the two doses versus placebo at week 24. The estimates will also be reported as odds ratios (versus placebo) of response.

10.4 Testing Strategy

A Bonferroni correction for multiple doses, and a two-step testing procedure applied to each dose separately will control the overall type 1 error at 5% for the testing of the primary-and key secondary endpoints. The null hypothesis of no difference in mean change from baseline to Week 24 in ADAS-Cog total score will be tested for each dose at significance level 2.5%. If the null hypothesis for ADAS-Cog is rejected for a dose, the null hypotheses of no difference in mean change from baseline at Week 24 for ADCS-ADL_{23} and mean ADCS-CGIC at Week 24 for the same dose will be tested applying Hochberg's testing procedure at significance level 2.5%. For demonstrating efficacy of a dose, ADAS-Cog and then either ADCS-CGIC or ADCS-ADL_{23} has to show statistically significant favourable differences compared to placebo at Week 24.

If ADAS-Cog and both ADCS-CGIC and ADCS-ADL_{23} are significant in the testing procedure of a dose, the 2.5% significance level from the testing of that dose will be transmitted to the testing of the other dose if that dose is not effective at the 2.5% significance level. Thus, in this scenario the testing procedure for the dose not significant at 2.5% significance level will be re-iterated at 5% significance level.

A summary table for the primary-and key-secondary endpoints will be presented with the estimated treatment differences, nominal p-values, and multiplicity adjusted p-values (i.e. the

lowest significance level under which the dose would meet the efficacy criterion based on the testing strategy).

10.5 Analysis of the Secondary Endpoints

Changes from baseline in NPI total score, changes from baseline in individual NPI items, changes from baseline in NPI total caregiver distress, changes from baseline in ADAS-Cog and ADCS- ADL_{23} composite score, changes from baseline in Basic ADCS-ADL_{23} and changes from baseline in Intrumental ADCS-ADL_{23} at week 4, 12, and 24 will be analysed using the same methodology as that described for the primary endpoint (see paragraph 10.2.1). Changes from baseline in NPI single items at Week 4, 12, and 24 in patients with an item score of at least 2 at baseline will also be analysed using the same methodology as that described for the primary endpoint.

Emergence of individual NPI items (score≥3) at Week 24 in patients with an item score of <3 at baseline will be compared for each dose versus placebo using a Cochran-Mantel-Haenszel test for comparing the proportion of patients with emerging symptoms stratifying for country and MMSE stratum using observed cases.

The proportion of patients with clinical response (ADAS-cog change ≤ -4 and ADCS-ADL_{23} change ≥0 and ADCS-CGIC<=4) at Week 24 will be compared for each dose versus placebo using a Cochran-Mantel-Haenszel test stratifying for country and MMSE stratum. The analysis will be done for observed cases, as well as by imputing missing values as non-response (NR). The corresponding analyses will be performed for the proportion of patients with response, where response is defined using cut-offs of ≤-3, ≤-2 , and ≤-1 for ADAS-Cog change and no deterioration in ADCS-ADL_{23} or ADCS-CGIC (ADCS-ADL_{23} change ≥0 and ADCS-CGIC<=4)

The proportion of patients with clinical worsening (ADAS-cog change ≥4 and ADCS-ADL_{23} change <0 and ADCS-CGIC >4) at Week 24 will be compared for each dose versus placebo using a Cochran-Mantel-Haenszel test stratifying for country and MMSE stratum. The analysis will be done for observed cases, as well as by imputing missing values as clinical worsening.

Change from baseline in MMSE score at Week 24 will be analysed using an ANCOVA model with treatment, country and MMSE stratum as fixed factors and baseline MMSE score as covariate using observed cases.

AUC from baseline to week 24 for the changes from baseline in ADAS-Cog total score, changes from baseline in ADCS-ADL_{23} total score, ADCS-CGIC minus 4, and changes from baseline in ADAS-Cog and ADCS-ADL_{23} composite score will be calculated by applying the trapezoidal rule to the least square mean estimates based the same model as in the primary analysis (see paragraph 10.2.1).[5] The cumulative treatment effects compared to placebo based on the AUC estimates will also be calculated.

Analyses of changes from baseline in EQ-5D, and VAS are decribed in chapter 13.

All analyses will be repeated by MMSE stratum.

11 Safety

11.1 Adverse Events

11.1.1 General Methodology for Adverse Events

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

All the tables and graphs will be presented by treatment group.

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order by the percentage of patients in the highest dose group of idalopirdine (60 mg).

Unless otherwise specified, the summaries of adverse events will include the total number and percentage of patients with an adverse event. Tables by preferred term and tables by SOC and preferred term will also include information about the total number of events. 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 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 treatment group, site, patient screening number, and adverse event start date and include preferred term, investigator term, adverse event start date, days since first dose of IMP, duration of the adverse event, date of death, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity, each intensity will be included.

11.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 17.1, or later.

11.1.3 Classification 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 prior to the date of first dose of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity at or after the date of first dose of IMP and for which *causality to IMP* not recorded as *Not Related – Prior to IMP*

For handling of missing or incomplete dates in the classification of adverse events, see paragraphs 18.4.1 (IMP start date) and 18.4.6 (adverse event start or stop dates).

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 All Adverse Events

All adverse events will be listed for the APRS.

An overview of the PYE to IMP (see definition in chapter 9), numbers, and percentages of patients with TEAEs, serious adverse events (SAEs), adverse events leading to withdrawal, or who died will be provided based on the APTS. For TEAEs, SAEs, and adverse events leading to withdrawal, the total number of events will be included.

11.1.5 Pre-treatment Adverse Events

Pre-treatment adverse events will be summarised by preferred term.

11.1.6 Treatment-emergent Adverse Events

The following summaries will be provided:
- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs with an incidence >5% in any treatment group by preferred term
- causally related TEAEs by preferred term
- TEAEs by intensity (*mild*/*moderate*/*severe*), and preferred term
- causally related TEAEs by intensity, and preferred term

The summary of TEAEs by SOC and preferred term will also be done by MMSE stratum.

11.1.7 Deaths

All adverse events with outcome death will be summarised.

All adverse events for patients who died will be listed.

11.1.8 Serious Adverse Events

All SAEs will be listed. SAEs occurring after the Completion/Withdrawal Visit will also be listed separately.

Treatment-emergent SAEs will be summarised by:
- SOC and preferred term
- 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:
- SOC and preferred term
- preferred term

11.1.10 Adverse Events of Special Interest

The following SMQs will be summarised in total and by preferred term:
- Convulsions (narrow scope)
- Drug related hepatic disorders (comprehensive search)
- Haemorrhages (broad scope)

Individual subject plots with the duration of each event during the *treatment period* for the preferred terms diarrhoea, vomiting and nausea will be presented. Intensity (mild, moderate, and severe) will be indicated by different grey colours, and first and last IMP intake will be marked in the plots.

11.2 General Methodology for Other Safety Data

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

All the tables and graphs will be presented by treatment group.

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

Descriptive statistics for the safety variables (lab tests, vital signs, weight, and ECGs), both for absolute values and changes from baseline, will be presented by visit week and the last assessment. All available assessments will be included in the identification of the last assessment (scheduled, re-assessments, and unscheduled).

The number and percentage of patients with at least one PCS value at any post-baseline assessment time point will be summarised by variable. All available assessments will be included in the evaluation of PCS values (scheduled, re-assessments, and unscheduled).

The number and percentage of patients with out-of reference range values and PCS values will be summaried by variable, and by visit week and last assessment.

For details about data handling issues, see paragraphs 18.1, and 18.3.2.

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

All adverse events for patients with PCS values will be listed by 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. The PCS value will be listed next to the corresponding adverse event(s); the PCS values and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

For selected variables, the following graphical presentations will be provided:

- box plots by visit week and the last assessment
- patient line plots with all available assessments. If relevant, out-of-reference-range and/or PCS values will be marked in the plot. Reference lines for reference ranges and/or PCS limits may also be included. If more than one value is available at a given assessment time point, the worst value will be used in the plots (maximum or minimum).

If relevant, shift tables displaying shifts from normal to PCS from baseline to post-baseline will be provided for for selected variables and include the numbers and percentages of patients.

11.3 Clinical Safety Laboratory Test Data

11.3.1 Data Presentation

The PCS criteria for the clinical safety laboratory tests are described in Table 2.

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, BILI, and EOSLE will be presented in a separate table, also including worst (highest) post-baseline assessment. All available assessments will be included in the evaluation of the worst assessment (scheduled, re-assessments, and unscheduled).

Graphical presentations of gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and 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, see paragraph 11.3.3). The graphs will be presented by treatment group, and sex.

Panel 3 Graphical Presentations for the Clinical Safety Laboratory Tests

Laboratory Test	Measure	Patient Selection	Line Plot	Box Plot
GGT, ALT, AST, ALP and total bilirubin	Absolute measure			√
GGT	Absolute measure	Patients with a post-baseline value out of upper reference range for GGT	√	
ALT	Absolute measure	Patients with a post-baseline value out of upper reference range for ALT	√	
AST	Absolute measure	Patients with a post-baseline value out of upper reference range for AST	√	
ALP	Absolute measure	Patients with a post-baseline value out of upper reference range for AP	√	
Total bilirubin	Absolute measure	Patients with a post-baseline value out of upper reference range for total bilirubin	√	

11.3.2 Urinalysis

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

The microscopy results will be listed for patients with any postive urine tests by assessment time point.

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

Signals of DILI will be assessed according to the FDA guideline.[6]

The number and percent of patients post-baseline in the categories below for AST/ALT, and AST and ALT separately will be summarized:

- 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 percent of patients post-baseline in the categories below for ALP and BILI will be summarized:

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

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

In the summaries, each patient should be counted only once using the worst post-baseline assessment.

Number and percent of patients fulfilling the joint criteria below post-baseline will be summarized:

- (Peak AST OR peak ALT>3xULN) AND peak BILI>2xULN AND peak ALP>1.5xULN
- (Peak ALT OR peak AST>3xULN) AND peak BILI>2xULN AND peak ALP≤1.5xULN
- Peak GGT>200 (IU/L) without (peak ALT OR peak AST OR peak ALP>2xULN)

Number and percent of patients with a post-baseline value ≥5% for B-eosinophils/leukocytes (ESOLE) will be summarized.

Evaluation of potential Drug-Induced Serious Hepatotoxicity (eDISH) will also be done by plots. Scatter plots of peak ALT/AST versus peak BILI (note that this means that the peak ALT/AST and the peak BILI may not occur at the same assessment timepoint). The values will be normalised by the ULN (unit xULN) and the X-and Y-axes will be on the 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 for each treatment group.

Subject line plots with values-by-time for ALT, AST, ALP , BILI, EOSLE, and GGT (overlaid in the same plot) will be generated for patients with ALT/AST > 1xULN. The test values will be normalised by the ULN (unit xULN) and the Y-axis will be on the log scale. The time will be days since baseline, and reference lines for the day of first-and last IMP intake 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.

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

- All patients
- Patienter with a post-baseline value of ALT/AST>2xULN
- Patienter with a post-baseline value of ALT/AST>3xULN

Patients with a post-baseline value of GGT, ALT, AST, ALP, BILI, or EOSLE>1xULN will be listed, and the listing will include all available ALT, AST, BILI, ALP, GGT, and EOSLE values, sorted by site, treatment group, subject number, assessment date and time.

11.4 Vital Signs and Weight

The PCS criteria for vital signs and weight are described in Table 3.

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	Box Plot
BMI	Absolute value			√
Weight	Percentage change from baseline	Patients with a post-baseline PCS low value	√	
Standing systolic BP	Absolute value			√
Standing diastolic BP	Absolute value			√
Standing pulse rate	Absolute value			√
Sitting systolic BP	Absolute value			√
Sitting diastolic BP	Absolute value			√
Sitting pulse rate	Absolute value			√

The box plot for BMI will include a reference line for underweight (BMI<18.5 kg/m2) and obesity (BMI>30 kg/m2).

11.5 ECGs

The PCS criteria for the ECG parameters are described in Table 4.

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

Panel 5 Graphical Presentations for ECG Parameters

Parameter	Measure	Patient Selection	Line Plot	Box Plot
Heart rate	Absolute value			√
QTcB	Absolute value			√
QTcB	Change from baseline	Patients with a post-baseline PCS value	√	
QTcF	Absolute value			√
QTcF	Change from baseline	Patients with a post-baseline PCS value	√	

11.6 Neurological Examinations

Shift tables for neurological examination findings displaying shifts from baseline to the Completion/Withdrawal Visit will be provided for each examination and combination and include the numbers and percentages of patients.

11.7 Other Safety Endpoint

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

The C-SSRS was assessed:

- for lifetime (using the Baseline Version) – the C-SSRS assessment obtained at screening Visit that collects a lifetime recall
- at baseline and post-baseline (Visit 3 to Visit 7) using the Since Last Visit Version

The summaries will be based on the APTS by treatment group for patients with at least one post-baseline C-SSRS assessment, regardless of whether they had a baseline C-SSRS 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* ar those who answered "No" to all items for *suicidal ideation* and *suicidal behaviour*. For each evaluation (lifetime, baseline, and post-baseline), 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 for each evaluation (lifetime, baseline, and post-baseline).

Panel 6 C-SSRS Items

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 *suicidal behaviour*, listings will be prepared including all C-SSRS scores; C-SSRS scores related to *suicidal behaviour* will be flagged.

12 Pharmacokinetic/Pharmacodynamic Analyses

Plasma concentrations of both idalopirdine and donepezil will be summarised by descriptive statistics by treatment group and visit.

A separate analysis plan describing the Pharmacokinetic/Pharmacodynamic analyses will be prepared by H. Lundbeck A/S: Dept of Quantitative Pharmacology in collaboration with Biostatistics Department and the results reported separately but referred to in the *Clinical Study Report*, as relevant.

13 Pharmacoeconomic Analyses

Dependence level score (based on the Dependence scale, see paragraph 18.2.8) will be summarised both as a continous and as a categorical variable. Absolute values and change from baseline values in EQ-5D utility score (see paragraph 18.2.7), EQ-5D VAS, dependence level score, and dependence total score (see paragraph 18.2.8) will be summarised by visit week and treatment group. Absolute values and shift from baseline in dependence level score and equivalent institutional care (dependence scale) will be summarised by visit week and treatment group. Note that the dependence scale was added as a pharmacoeconomic assessment in protocol amendment PA02.

The RUD Lite items will be summarised by visit week and treatment group.

Changes from baseline in EQ-5D utility Score and EQ-5D VAS at week 12, and 24, will be analysed using the same methodology as that described for the primary endpoint (see paragraph 10.2.1).

Increase from baseline in dependence level score will be defined as a binary variable (1 if change from baseline in dependence level score>0) at week 12 and 24, and compared for each dose versus placebo using a Cochran-Mantel-Haenszel test stratifying for country and MMSE stratum. The analysis will be done for observed cases.

All analyses will be repeated by MMSE stratum.

Further presentations and statistical analyses of pharmaco-economics will be detailed in a separate Pharmaco-Economic Statistical Analysis Plan, prepared by the Global Analytics department, H. Lundbeck A/S, prior to unblinding. The results of the pharmaco-economic analyses described in the Pharmacoeconomic SAP will be presented in a separate pharmacoeconomic report.

14 Interim Analyses

No interim analyses for efficacy was planned. An independent DMC monitored the safety data at regular intervals specified in the Data Monitoring Committee Charter.

15 Sample Size Considerations

In total, 310 patients will be randomized to each arm providing a power of ~90% for at least one dose showing significant improvements on an overall 5% level on both ADAS-Cog and at least one of ADCS-ADL_{23} or ADCS-CGIC, assuming improvements of 2 points on both ADAS-Cog and ADCS-ADL_{23}, and 0.25 on ADCS-CGIC for both doses. The SDs are approximately 6.10, 9.15, and 1.15 for the three outcomes when adjusting for intra-patient correlation and drop-out. The SD for each endpoint is obtained from the number of patients randomized in each arm (N1 and N2) and the standard error (SE) of the treatment effect estimate at 24 weeks in 12936A as $SD=SE/\sqrt{(1/N1+1/N2)}$. This estimate both takes into account the actual variance at 24 weeks and the loss of information due to drop-out during the study, assuming that the dropout pattern observed in 12936A is representative of what will be observed in this study. The estimated correlations between the endpoints are -0.27 between ADAS-Cog and ADCS-ADL_{23}, 0.38 between ADAS-Cog and ADCS-CGIC, and -0.35 between ADCS-ADL_{23} and ADCS-CGIC when adjusting for baseline scores. Multiplicity due to multiple doses and endpoints is adjusted for as explained in paragraph 10.4. The power has been evaluated by simulation from a multivariate normal distribution with the assumed mean and covariance structure described.

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 2.2 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

The following endpoints were added:

- Endpoints addressing the secondary objective:
  - Change from baseline to Week 24 in NPI single items in patients with an item score of at least 2 at baseline
  - Change from baseline in NPI caregiver distress total score

- Endpoints that are supportive of the primary objective:
  - Clinical response at Week 24 where response is defined using cut-offs of ≤-3, ≤-2 , ≤-1 for ADAS-cog change, ADCS- ADL_{23} change ≥0 and ADCS-CGIC<=4
  - Area under curve (AUC) from baseline to week 24 for the changes from baseline in ADAS-Cog total score
  - AUC from baseline to week 24 for the changes from baseline in ADCS- ADL_{23} total score
  - AUC from baseline to week 24 for the ADCS-CGIC minus four (as ADCS-CGIC is an assessment of changes, i.e. no change in health state corresponds to a score of 0)
  - Changes from Baseline to Week 24 in ADAS-Cog and ADCS-ADL_{23} composite score
  - AUC from baseline to week 24 for the changes from baseline in ADAS-Cog and ADCS- ADL_{23} composite score
  - Change from Baseline to Week 24 in Basic ADCS- ADL_{23}
  - Change from Baseline to Week 24 in Instrumental ADCS- ADL_{23}

Note that the endpoint *Change from baseline to Week 24 in NPI Anxiety item score in patients with an NPI Anxiety score of at least 2 at baseline* in the protocol is included in *Change from baseline to Week 24 in NPI single items in patients with an item score of at least 2 at baseline.*

Analyses of the added endpoints are described in paragraph 10.5.

The endpoint *Emergence of individual NPI items (score>0)* for patients with an item score of 0 at baseline was replaced by:

- Emergence of individual NPI items (score ≥3). The analyses will be based on patients with an item score of <3 at baseline.

All CIs will be presented at the 95% confidence level.

Sensitivity analyses with country replaced by grouped site in the primary analysis were added for the primary-and key-secondary endpoints (see paragraph 10.2.4 and 10.3.4).

Sensitivity analyses with MMSE total score at baseline as a continuous covariate, and MMSE total score at baseline-by-week interaction also included in the primary model were added for the primary-and key-secondary endpoints (see paragraph 10.2.4 and 10.3.4).

Subgroup analyses of apathy (Yes/No), where apathy is defined as NPI item apathy score>0 at baseline, and age (<85, and ≥ 85) were added for the primary-and key-secondary endpoints (see paragraph 10.2.3 and 10.3.3).

Instead of the specification of the model for the non-linear mixed model for ordinal response, a logistic regression analysis for the outcome at week 24 was specified as a sensitive analysis for ADCS-CGIC. This was due to technical challenges anticipated with fitting the non-linear mixed model for the repeated measures and imposed restrictions on the marginal correlation structure for these with this approach. In addition, the projected relative low withdrawal rate justifies the use of the simpler logistic model for observed cases at week 24 for sensitivity analysis. The model will use a logit link function to relate the underlying latent variable to the probability of observing a response less than or equal to a given ordered response (see paragraph 10.3.4).

The testing strategy was extended. If ADAS-Cog and both ADCS-CGIC and ADCS-ADL23 are significant in the testing procedure of a dose, the 2.5% significance level from the testing of that dose will be transmitted to the testing of the other dose if that dose is not effective at the 2.5% significance level.

18 Details on Data Handling

18.1 Definition of Baseline

The baseline value will be defined as the value captured either at the Screening Visit or at the Baseline Visit, whichever comes later.

18.2 Derived Variables

18.2.1 MMSE Total Score and MMSE Stratum

MMSE contains 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 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): ADCOG11 ADCOG12	Total number of words identified **incorrectly**, where scores>12 truncated to 12 (ranges 0-12): 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, Basic ADCS-ADL$_{23}$, and Instrumental ADCS-ADL$_{23}$

The ADCS-ADL$_{23}$ scale contains of 23 item scores (Usual Eating Performance, Optimal Walking Performance, Usual Bowel/Bladder Function, Usual Bathing Performance, Optimal Grooming Performance, Dressing, Use a Telephone, Watch Television, Pay Attention to Conversation, Clear Dishes, Find Belongings, Obtain Beverage, Make a Meal, Dispose of Garbage, Get Around Outside Home, Go Shopping, Keep Appointments, Left On His/Her Own, Talk About Current Events, Read More Than 5 Minutes, Write Things Down, Perform Pastime, and Use Household Appliance), 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 Definition of ADCS-ADL$_{23}$ Item Scores

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.

Basic ADCS-ADL_{23} is defined as the sum of the item scores 1 to 6 (Usual Eating Performance, Optimal Walking Performance, Usual Bowel/Bladder Function, Usual Bathing Performance, Optimal Grooming Performance, and Dressing), and Instrumental ADCS-ADL_{23} is defined as the sum of the item scores 7 to 23. Basic-and Instrumental ADCS-ADL_{23} will be calculated after the imputation rule for missing item scores have been applied for the calculation of the ADCS-ADL_{23} total score. The basic ADCS-ADL_{23} ranges from 0 to 22, and Instrumental ADCS-ADL_{23} ranges from 0 to 56.

18.2.4 ADAS-Cog and ADCS-ADL_{23} Composite Score

The composite score for ADAs-Cog and ADCS-ADL_{23} will be constructed by averaging the standardized scores (z-scores) for each scale, i.e. equal weights will be used for the scales. The z-scores for each scale will be computed by subtracting the mean total score at baseline from the individual subject total score and dividing by the standard deviation (SD) for the total score at baseline. In the calculation of the composite score, the sign for the z-score of ADAS-Cog will be reversed (-1*z-score), i.e. a positive composite score indicates an improvement.

18.2.5 NPI Total Score

The NPI scale contains 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.

18.2.6 NPI Caregiver Distress Total Score

The NPI caregiver distress total score is calculated as the sum of the caregiver distress for each domain (aCRF NPI05, ranging from 0 to 5), and ranging from 0 to 60.

If caregiver distress for four or more domain domains are missing, the NPI caregiver distress total score will be missing. If less than four scores are missing, the missing doimains will in the calculation of the NPI caregiver distress total score be imputed by the mean of the non-missing scores, rounded to the closest integer (.5 rounded upwards).

18.2.7 EQ-5D Utility Score

The EQ-5D utility score will be derived from the EQ-5D questionnaire items mobility (aCRF EQ5DP01), self care (aCRF EQ5DP02), activity (aCRF EQ5DP03), pain (aCRF EQ5DP04), and anxiety (aCRF EQ5DP01). All items are scored from 1 (no problems) to 3 (extreme problems). If one ore more item score is missing, the utility score will be missing. The utility score will be calculated according to Doulan P. et al. using the SAS code below. [7]

```
DATA eq5d;

    SET eq5d;

    IF (EQ5DP01 NOT IN (1,2,3) OR EQ5DP02 NOT IN (1,2,3) OR

    EQ5DP03 NOT IN (1,2,3) OR EQ5DP04 NOT IN (1,2,3) OR

    EQ5DP05 NOT IN (1,2,3)) THEN EQ5D_utility=.;

    ELSE DO;

        IF (SUM(OF EQ5DP01-EQ5DP05))=5 THEN c0=0;

        ELSE c0=0.081;

        IF (EQ5DP01=1) then c1=0;

        ELSE IF (EQ5DP01=2) THEN c1=0.069;
```

```
        ELSE IF (EQ5DP01=3) THEN c1=0.314;

        IF (EQ5DP02=1) THEN c2=0;

        ELSE IF (EQ5DP02=2) THEN c2=0.104;

        ELSE IF (EQ5DP02=3) THEN c2=0.214;

        IF (EQ5DP03=1) THEN c3=0;

        ELSE IF (EQ5DP03=2) THEN c3=0.036;

        ELSE IF (EQ5DP03=3) THEN c3=0.094;

        IF (EQ5DP04=1) THEN c4=0;

        ELSE IF (EQ5DP04=2) THEN c4=0.123;

        ELSE IF (EQ5DP04=3) THEN c4=0.386;

        IF (EQ5DP05=1) THEN c5=0;

        ELSE IF (EQ5DP05=2) THEN c5=0.071;

        ELSE IF (EQ5DP05=3) THEN c5=0.236;

        IF (MAX(OF EQ5DP01-EQ5DP05)=3) THEN c6=0.269;

        ELSE c6=0;

        EQ5D_utility=1-SUM(OF c0-c6);

    END;

RUN;
```

18.2.8 Dependence Level Score and Dependence Total Score

The dependence level score, ranging from 0 (no dependence) to 5 (complete dependence), is based on the 13 items of the Dependence scale described in Panel 9.

Panel 9 Items Dependence Scale

Item	aCRF variable and codes
Does the patient need reminders or advice to manage chores, do shopping, cooking, play games, or handle money?	DS01 0=No 1=Occasionally 2=Frequently
Does the patient need help to remember important things such as appointments, recent events, or names of family or friends?	DS02 0=No 1=Occasionally 2=Frequently
Does the patient need frequent (at least once a month) help finding misplaced objects, keeping appointments, or maintaining health or safety (locking doors, taking medication)?	DS03 0=No 1=Yes
Does the patient need household chores done for them?	DS04 0=No 1=Yes
Does the patient need to be watched or kept company when awake?	DS05 0=No 1=Yes
Does the patient need to be escorted when outside?	DS06 0=No 1=Yes
Does the patient need to be accompanied when bathing or eating?	DS07 0=No 1=Yes
Does the patient have to be dressed, washed, and groomed?	DS08 0=No 1=Yes
Does the patient have to be taken to the toilet to avoid incontinence?	DS09 0=No 1=Yes
Does the patient have to be fed?	DS10 0=No 1=Yes
Does the patient need to be turned moved, or transferred?	DS11 0=No 1=Yes
Does the patient wear a diaper or a catheter?	DS12 0=No 1=Yes
Does the patient need to be tube fed?	DS13

	0=No 1=Yes

If one or more item scores are missing, the dependence level score will be missing. The dependence level score will be calculated using the SAS code below:

```
Data eff_DS_nom;

    set eff_DS_nom;

    if
nrmiss(DS01,DS02,DS03,DS04,DS05,DS06,DS07,DS08,DS09,DS10,DS11,DS12,DS13))>0
then ds_TOT=.;

    else if DS11=1 or  DS12=1 or DS13=1 then ds_TOT=5;

    else if DS08=1 or DS09=1 or DS10=1 then DS_TOT=4;

    else if DS05=1 or DS06=1 or DS07=1 then DS_TOT=3;

    else if ((DS01=1)+( DS02=1)+(DS03=1)) >=2 or DS01=2 or DS02=2 or DS04=1 then
    DS_TOT=2;

    else if DS01=1 or DS02=1 or DS03=1 then DS_TOT=1;

    else DS_TOT=0;

run;
```

The dependence total score is defined as the sum of the 13 items, ranging from 0 to 15. If one or more item scores are missing, the dependence total score will be missing.

18.3 Assigning Data to Visits

This paragraph describes rules for data to be used in descriptive analyses by visit week, and statistical analyses.

18.3.1 Rating Scales

The assessment at the Withdrawal Visit for patients who withdraw from treatment will be assigned to a nominal visit in the *Treatment period* according to the visit windowing specified in Panel 10 (ADAS-Cog, ADCS-CGIC and ADCS-ADL_{23}, and NPI), or Panel 11 (RUD Lite, EQ-5D, and Dependene Scale). The assessment collected at the scheduled visit will be used in the analyses, or the windowed assessment from the Withdrawal Visit if no scheduled 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.

Panel 10 Visit Windows for assessments collected at Visit 3, Visit 5, and Visit 7

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V3	4	28	1 to 55
V5	12	84	56 to 125
V7 (Completion/Withdrawal)	24	168	>125

Panel 11 Visit Windows for assessments collected at Visit 5, and Visit 7

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V5	12	84	1 to 125
V7 (Completion/Withdrawal)	24	168	>125

The efficacy assessments collected at the Withdrawal Follow-up Visit, and Drop-out Retrieval Visit will only be included in a sensitivity analysis. Assessments at the Withdrawal Follow-up Visit will be assigned to a nominal visit in the *treatment period* according to the visit windowing specified in Panel 10. Assessments at the Drop-out Retrieval Visit will by definition be assigned to Visit Week 24. If there are more than one assessment assigned to the same visit, the priority rule for the assessment to be used in the sensitivity analysis will be Drop-out Retrieval Visit, Withdrawal Follow-up Visit, Withdrawal Visit, and scheduled Visit.

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 *Treatment period*, according to the visit windowing specified in Panel 12.

Panel 12 Visit Windows for Clinical Safety Data

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V3	4	28	1 to 41
V4	8	56	42 to 69
V5	12	84	70 to 104
V6	18	126	105 to 146
V7 (Completion/Withdrawal)	24	168	>146

For assessments at the Screening Visit or at the Baseline 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 in the analyses by visit, or the windowed assessment from the Withdrawal Visit if no scheduled assessment is available.

18.4 Handling of Missing or Incomplete Dates/Times

18.4.1 IMP Start and Stop Dates

For patients in the APTS, missing IMP start date will be imputed with the randomisation 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 Donepezil Start Date

Donepezil treatment before baseline (screening Visit) was recorded, where each change in dose, frequency, or route of administration in donepezil treatment prior to baseline was recorded as a new event.

Duration in years of donepezil treatment is calculated as number of days between start date of the first recorded donepezil treatment and the screening Visit divided by 365.25. In the calculation of duration, missing start month will be imputed by June, and missing start day will be imputed by 15, and then the minimum of imputed start dates, complete start dates, and the date of screening Visit will be used as start date.

18.4.3 Date of Alzheimer Diagnosis

Duration of Alzheimer diagnosis at baseline will be calculated as the number of days between the date of diagnosis and the screening Visit divided by 365.25. In the calculation of duration, missing month of diagnosis will be imputed by June, and missing day of diagnosis will be imputed by 15, and then the minimum of the imputed date of diagnosis and the date of the screening Visit will be used as date of diagnosis.

18.4.4 Withdrawal Date

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

18.4.5 Medication Start and Stop Dates

Handling of missing medication start-or stop dates are described in Panel 13.

Panel 13 Handling of Missing Dates in Classification of Medications

Medication Start Date	Medication Stop Date	Medication Classification
Unknown	< date of first dose of IMP	Discontinued prior to first dose of IMP
Unknown	≥ date of first dose of IMP	Started at or after first dose of IMP
< date of first dose of IMP	Unknown	Continued after first dose of IMP
≥ date of first dose of IMP	Unknown	Started at or after first dose of IMP
Unknown	Unknown	Started at or after first dose of IMP

18.4.6 Adverse Event Start and Stop Dates

If a stop date is missing due to an event being ongoing, 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 start date is missing or incomplete, and the stop date is prior to the first dose of IMP, or the stop date is incomplete but known to be prior to the first dose of IMP (stop day is missing and stop year and month is before the year and month of the first dose of IMP, or stop day and month are missing and stop year is before the year of first dose of IMP).
- The start date is incomplete but known to be prior to the first dose of IMP (start day is missing and start year and month is before the year and month of the first dose of IMP, or start day and month are missing and start year is before the year of first dose of IMP), and no change in intensity.

In all other cases of an adverse event with a missing or incomplete start or stop date, the event will be classified as a TEAE.

18.5 Compliance

In the calculation of compliance with IMP in visit intervals, the Withdrawal Visit will be assigned to the closest scheduled visit not attended for withdrawn patients.

Compliance with IMP is reported since the previous visit. Therefore, if one or more visit has been missed between two visits, the compliance with IMP for visit interval(s) in a period including missed visit(s) will be estimated by the compliance with IMP in the period.

If compliance reporting is missing at the last attended visit in the *treatment period* all days since the previous visit will be assumed to be non-compliant, and the number of days since previous visit will be added to the total number of days of non-compliance in the calculation of compliance.

18.6 Grouping of Small Countries and Sites

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

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

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

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

References

1. Siddiqui O, Hung HMJ, O'Neill R. MMRM vs. LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat. 2009; 19: 227-246.
2 . Ayele B, Lipkovich I, Molenberghs G, and Mallinckrodt C. Multiple-Imputation-Based Approach to Sensitivity Analyses and Effectiveness Assessments in Longitudinal Clinical Trials, J Biopharm Stat. 2014; 24: 211–228
3. Little R, Yau L. Intent-to-treat analysis for longitudinal studies with drop-outs. Biometrics. 1996; 52: 1324-1333.
4. Rubin D. Multiple imputation for nonresponse in surveys. New York: Wiley; 1997.
5. Alireza Atri, Suzanne B Hendrix, Pejović V, Hofbauer R, Edwards J, Molinuevo J, and Graham S. Cumulative, additive benefits of memantine-donepezil combination over component monotherapies in moderate to severe Alzheimer's dementia: a pooled area under the curve analysis. Alzheimers Res Therapy December 2015, 7:28
6. United States Food and Drug Administration (FDA). Guidance for Industry: Drug-induced liver injury Premarketing Clinical Evaluation. July 2009.
7. Doulan P, Gudex C, Kind P. A social tariff for EuroQol: Results from a UK general population survey. Discussion paper No. 138. Centre for health economics, University of New York, 1995.

Appendix I

Statistical Analysis Plan

Authentication and Authorisation

Statistical Analysis Plan
Authentication and Authorisation

Study title:	Randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with donepezil; study 1
SAP date:	29 April 2016

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

Authentication

Biostatistician:	Anna Bladström
CRS:	Neli Boneva, CRD Neurology Idalopirdine Team

Authorisation

Head, Biostatistics:	Anna Karina Trap Huusom

Appendix II

Study Flow Chart

Study Flow Chart

Table 1 Study Procedures and Assessments

Visit	Screening	Base-line	Treatment Period				Completion[a]/ Withdrawal[b]	Safety/ Withdrawal Follow-up[c]	Drop-out Retrieval[m]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Day/[d]	**-14/-1**	**0**	**28/**	**56/**	**84/**	**126/**	**168/**	**196/**	**168/**
End of Week			**4**	**8**	**12**	**18**	**24**	**28**	**24[n]**
Visit Window[e] (days relative to nominal visit)			**± 7d**	**±7d**	**± 7d**	**± 7d**	**±7d**	**+ 7d**	**±7d**
Screening/Baseline Procedures and Assessments									
Signed informed consent	√								
Diagnosis NINCDS-ADRDA	√								
MMSE	√	√					√		
Disease-specific history	√								
NINDS-AIREN	√								
Relevant history (social, medical, psychiatric, neurological)	√								
Years of education	√								
Magnetic resonance imaging / Computerised tomography[f]	√								
Demographics (age, sex, race)	√								
Nicotine and alcohol use	√								
Height	√								
CYP enzyme and ApoE genotyping		√							
Inclusion/exclusion criteria	√	√							
Randomisation		√							
Efficacy Assessments									
ADAS-cog	√	√	√		√		√	√[g]	√
ADCS-ADL_{23}		√	√		√		√	√[g]	√
ADCS-CGIC		√	√		√		√	√[g]	√
NPI		√	√		√		√		
Other Assessments									
RUD Lite		√			√		√		

Visit	Screening	Base-line	Treatment Period				Completion[a]/ Withdrawal[b]	Safety/ Withdrawal Follow-up[c]	Drop-out Retrieval[m]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Day/[d]	**-14/-1**	**0**	**28/**	**56/**	**84/**	**126/**	**168/**	**196/**	**168/**
End of Week			**4**	**8**	**12**	**18**	**24**	**28**	**24[n]**
Visit Window[e] (days relative to nominal visit)			**± 7d**	**±7d**	**± 7d**	**± 7d**	**±7d**	**+ 7d**	**±7d**
EQ-5D		√			√		√		
Dependence scale		√			√		√		
Safety Assessments									
Adverse events[h]	√	√	√	√	√	√	√	√[i]	√[o]
Blood and urine sampling for clinical safety laboratory tests	√	√	√	√	√	√	√		
Vital signs, weight, ECGs	√	√	√	√	√	√	√		
C-SSRS	√	√	√	√	√	√	√		
Examinations (physical, neurological)	√	√		√		√	√		
Pharmacokinetic/Pharmacodynamic Assessments									
Blood sampling for Lu AE58054 and donepezil		√	√	√	√	√	√		
Exploratory Biomarker Assessments									
Blood sampling for gene expression profiling[j]		√							
Blood sampling for metabolomics/proteomics[j]		√							
Blood sampling for pharmacogenetics (optional)[k]		√							
Other Study Procedures									
IMP dispensed		√	√	√	√	√			
IMP returned and IMP accountability			√	√	√	√	√		
Recent and concomitant medication	√	√	√	√	√	√	√	√	√[p]
Dispense Patient Identification card		√							
Patient Identification card returned							√[l]		

a. Patients completing the 24 week Treatment Period may be eligible to enter a 6-month open-label extension study with idalopirdine and donepezil.

b. This visit should take place as soon as possible after the patient withdraws from the study.

c. Patients who complete the study without entering the open-label extension study will have a Safety Follow-up Visit (no efficacy assessments) 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. This follow-up will include safety and selected efficacy assessments. Patients who withdraw their consent should still have a safety follow-up (without efficacy assessment) 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.
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 randomisation/baseline. The number of days between two visits (except for the Drop-out Retrieval Visit) must not exceed the number of days for which IMP is provided in the wallet cards.
f. A scan performed within the previous 12 months may be used to assess eligibility. If no such scan is available, the Magnetic Resonance Imaging (MRI)/Computerised tomography (CT) should be performed at the Screening Visit or between the Screening and the Baseline visit. No central reading will be done.
g. Efficacy assessments only for patients withdrawn.
h. Signs and symptoms present at screening and/or baseline (before IMP intake) must be recorded on an *Adverse Event Form*.
i. Only for adverse events ongoing at Completion/Withdrawal and new SAEs
j. Sampling for drug bioanalysis, exploratory gene expression profiling (mRNA) and metabolomics/proteomics is an integrated part of the study and is covered by the main Patient Information Sheet. These blood samples should preferably be collected with the safety laboratory samples, as appropriate.
k. Sampling for pharmacogenetics is optional and a separate Patient Information Sheet covers this analysis. This sampling should preferably be at the Baseline Visit but may be collected at any visit that includes a clinical safety laboratory sample.
l. 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.
m. Withdrawn patients, except for those who withdraw their consent or discontinue their participation to the study at or after week 18 (Visit 6), will be scheduled for a Drop-out Retrieval Visit.
n. Projected Week 24 visit, the visit that the patient should have been attending, provided he/she had not been withdrawn from the study.
o. Only for adverse events ongoing at previous visit and new SAEs that are considered by the investigator related to the study medication.
p. Only for concomitant medications ongoing at the day of the Drop-out Retrieval Visit.

Appendix III

SAS® Code

SAS® Code

The SAS code for the primary MMRM-analysis 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;
    lsmeans armcd*analysis_week/ diff cl alpha=0.05;
run;
```

The SAS code for the sensitivity analysis using a pattern mixture model will be:

```
%**Prepare data on the form needed for proc MI: one column for each visit Week 4, 12, and
24;

proc transpose data=ADAS out=ADAS_w prefix=ADASTOT_DL_w;
    var ADASTOT_DL;
    by usubjid country armcd MMSSTR ADASTOT_BL COMPLFL lastweek;
    id analysis_week;
run;


%**Impute non-monotone missing observation to make sure that datasets only has monotone
missing values left;

proc sort data = ADAS_w;
```

```
      by armcd MMSSTR;
run;


proc mi data = ADAS_w out = AllMono nimpute = 200 seed = 17345;
      by armcd MMSSTR;
      var  ADASTOT_BL ADASTOT_DL_w4 ADASTOT_DL_w12 ADASTOT_DL_w24;
      mcmc chain = multiple impute = monotone;
      ods output MissPattern=mp;
run;


%**Impute monotone missing values, using pattern in the placebo group (armcd='A');
%*** Do one imputation per imputed dataset from previous step, i.e nimpute=1 in this step;
proc mi data=AllMono seed=4387410 nimpute=1 out=out_mi;
   class armcd country MMSSTR;
   monotone reg ();
   mnar model( ADASTOT_DL_w4 ADASTOT_DL_w12 ADASTOT_DL_w24 /modelobs=
(armcd='A')); * use mnar specification to impute from a model determined by the modelobs=
parameter;
   var  country MMSSTR ADASTOT_BL ADASTOT_DL_w4 ADASTOT_DL_w12
ADASTOT_DL_w24;
run;


%**Prepare data for MMRM analysis ;
%**If not withdrawn from treatment (COMPLFL=1), imputed monotone values will be re-set
to missing;
%**Note, lastweek is >=4, since analysis will be based on the same patients as in the primary
analysis
```

```
where patients without valid post-baseline obs are excluded;
data out_mi_Anl(drop=ADASTOT_DL_w4 ADASTOT_DL_w12 ADASTOT_DL_w24);
      set out_mi;
      analysis_week=4 ;
      ADASTOT_DL=ADASTOT_DL_w4;
      output;
      analysis_week=12 ;
      if complfl=1 and lastweek=4 then ADASTOT_DL=.;
      else ADASTOT_DL=ADASTOT_DL_w12;
      output;
      analysis_week=24 ;
      if complfl=1 and lastweek IN (4 12) then ADASTOT_DL=.;
      else ADASTOT_DL=ADASTOT_DL_w24;
      output;
run;
proc sort data=out_mi_Anl;
      by _Imputation_
      analysis_week;
run;

%**MMRM-analysis by imputed datasets using the same model as in the primary analysis;
proc mixed noclprint data = out_mi_Anl ic method=REML;
      by _imputation_;
      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;

    lsmeans Armcd*analysis_Week/ diff cl alpha=0.05;

    ods output diffs=MIdiffs;

    ods output LSMeans=MILSM;

run;


%**Combines the results  of the analyses of the 200 complete datasets generated by
simulations;

%**Note that the treatment effect is reversed (PBO-active);

proc sort data=MIdiffs(where=(analysis_week=24 and analysis_week=_analysis_week  and
armcd='A')) out=MIdiffs2;

    by _armcd;

run;

proc mianalyze parms= MIdiffs2;

    by _armcd;

    modeleffects armcd*analysis_week ;

    ods output ParameterEstimates = MIdiffs_ana;

run;
```

Appendix IV

PCS Criteria

PCS Criteria

Table 2 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 3 PCS Criteria for Vital Signs and Weight

CDISC term	Parameter (units)	PCS Low	PCS 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 (beats/min)	≤ 50 and decrease ≥ 15	≥ 120 and increase ≥ 15

Table 4 PCS Criteria for ECG Parameters

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