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### 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 Study Protocol Edi. 3.0

**Study Number** 14861A

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## Clinical Study Protocol

### **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**

### **Lu AE58054**

### **Phase III**

Study No.: 14861A

EudraCT/IND No.: 2012-004763-45 / 118,782

Sponsor: H. Lundbeck A/S (Lundbeck)  
2500 Valby (Copenhagen), Denmark

Edition No.: 3.0 (including PA01, PA02 and CSPA01)  
(the version No. in the footer is the system version No.)

Date of edition: 28 February 2014

Edition history: Edition 1.0 (original protocol)  
Edition 2.0 (Protocol 2.0 including PA01 and CSPA01)

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## Synopsis – Study 14861A

<b>Sponsor</b> H. Lundbeck A/S	<b>Investigational Medicinal Product</b> Lu AE58054	<b>EudraCT/IND No.</b> 2012-004763-45 / 118,782
<b>Title of Study</b> 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		
<b>Study Sites and Number of Patients Planned</b> 120 sites are planned in 15-20 countries, hospital and specialist centres 930 randomised patients are planned with 310 patients per treatment group		
<b>Objectives</b> Primary objective: <ul style="list-style-type: none"> <li>- To establish efficacy of Lu AE58054 as adjunctive therapy to donepezil for symptomatic treatment of patients with mild-moderate Alzheimer's disease.</li> </ul> Secondary objective: <ul style="list-style-type: none"> <li>- To investigate the effect of Lu AE58054 as adjunctive therapy to donepezil on neuropsychiatric symptoms in patients with mild-moderate Alzheimer's disease.</li> </ul> Other objectives: <ul style="list-style-type: none"> <li>- To explore population pharmacokinetics (PK)/pharmacodynamics (PD).</li> </ul> Safety objectives: <ul style="list-style-type: none"> <li>- To evaluate the safety and tolerability of Lu AE58054 as adjunctive therapy to donepezil in patients with mild-moderate Alzheimer's disease.</li> </ul>		
<b>Study Methodology</b> This is an interventional multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study of Lu AE58054 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 study will include the following periods: 2-week screening period 24-week double-blind (Lu AE58054 30 or 60 mg/day or placebo) treatment period as add-on to donepezil 10 mg/day 4-week safety follow-up period Patients will be randomised via a centralised randomisation system (Interactive Voice Response System [IVRS]). Randomisation will be stratified by Mini Mental State Exam (MMSE) stratum (<19, ≥19). Randomisation will be restricted such that at most 50% of the patients are in the MMSE 19-22 stratum. The study design is presented in Panel 1 and the scheduled assessments are summarised in Panel 2. An independent Data Monitoring Committee (DMC) will monitor the patients' safety according to the <i>Data Monitoring Committee Charter</i> .		

### Target Patient Population

#### • Major inclusion criteria

The patient has probable AD diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

The patient has a Mini Mental State Examination (MMSE) score at screening of at least 12 and no greater than 22.

The patient is a man or woman, aged at least 50 years.

The patient has been treated daily with donepezil for at least 6 months prior to the Screening Visit. The dose has been stable at 10 mg/day for the last 4 months prior to screening and throughout the screening period.

#### Major exclusion criteria

The patient has been treated with any investigational product within 60 days or 5 half-lives (whichever is longer) prior to the Screening Visit.

The patient has been treated with anti-Amyloid Beta or anti-Tau Protein monoclonal antibodies or other disease modifying strategies within one year prior to the Screening Visit.

The patient has been treated with an active vaccine targeting Amyloid Beta or Tau Protein.

The patient has evidence of any clinically significant neurodegenerative disease or other serious neurological disorders other than AD including but not limited to Lewy body dementia, fronto-temporal dementia, Parkinson's disease, Huntington's disease, major cortical stroke, major head trauma, primary or secondary cerebral neoplasia or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning.

The patient has a history of seizures, with the exception of febrile seizures in childhood.

The patient has clinical and radiological findings that fulfil the standards of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia.

The patient's donepezil therapy is likely to be interrupted or discontinued during the study.

The patient is currently receiving memantine or has taken memantine within 2 months prior to the Screening Visit.

The patient has been tested positive for human immunodeficiency virus (HIV).

The patient has been tested positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus /antibodies (anti-HCV) AND has abnormal ALT, AST or bilirubin at the Screening Visit.

The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:

- a serum creatinine value >1.5 times the upper limit of the reference range, or
- a serum total bilirubin value >1.5 times the upper limit of the reference range, or
- a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >1.5 times the upper limit of the reference range

### Investigational Medicinal Products, Doses and Modes of Administration

Base treatment:

Donepezil hydrochloride - 10 mg/day; once daily, tablets, for oral use.

IMP:

Lu AE58054 - two doses: 30 mg/day and 60 mg/day; once daily, encapsulated tablets, for oral use.

Placebo - once daily, matching placebo capsules, for oral use.

<p><b>Efficacy Assessments</b></p> <ul style="list-style-type: none"><li>• Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)</li><li>• Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC)</li><li>• Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL<sub>23</sub>) total score</li><li>• Neuropsychiatric Inventory (NPI) total score</li><li>• Mini Mental State Examination (MMSE)</li></ul>
<p><b>Pharmaco-economic Assessments</b></p> <ul style="list-style-type: none"><li>• Resource Utilisation in Dementia Lite (RUD Lite)</li><li>• EQ-5D-3L, a measure of health-related quality of life.</li><li>• Dependence scale</li></ul>
<p><b>Pharmacokinetic Assessments</b></p> <p>Blood samples for drug plasma concentration analyses of Lu AE58054 and donepezil will be drawn according to the schedule in Panel 2.</p>
<p><b>Safety Assessments</b></p> <ul style="list-style-type: none"><li>• Adverse events (AEs)</li><li>• Clinical safety laboratory tests</li><li>• Vital signs</li><li>• Weight/BMI</li><li>• Electrocardiograms (ECGs)</li><li>• Physical and neurological examinations</li><li>• Columbia Suicide Severity Rating Scale (C-SSRS)</li></ul>
<p><b>Endpoints</b></p> <p>Endpoints addressing the primary objective:</p> <ul style="list-style-type: none"><li>• Primary endpoint:<ul style="list-style-type: none"><li>– Cognition:<ul style="list-style-type: none"><li>• Change from baseline to Week 24 in Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog)</li></ul></li></ul></li><li>• Key secondary endpoints:<ul style="list-style-type: none"><li>– Global impression:<ul style="list-style-type: none"><li>• Alzheimer's disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) score at Week 24</li></ul></li><li>– Function:<ul style="list-style-type: none"><li>• Change from baseline to Week 24 in Alzheimer's disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL<sub>23</sub>) total score</li></ul></li></ul></li><li>• Secondary endpoints:<ul style="list-style-type: none"><li>– Endpoints addressing the secondary objective:<ul style="list-style-type: none"><li>• Change from baseline to Week 24 in Neuropsychiatric Inventory (NPI) total score</li><li>• Change in single NPI items at Week 24</li><li>• Change from baseline to Week 24 in NPI Anxiety item score in patients with an NPI Anxiety score of at least 2 at baseline</li></ul></li><li>– Endpoints that is supportive of the primary objective<ul style="list-style-type: none"><li>• Clinical response at Week 24 (ADAS-cog change <math>\leq -4</math> and ADCS-ADL<sub>23</sub> change <math>\geq 0</math> and ADCS-CGIC <math>\leq 4</math>)</li><li>• Clinical worsening at Week 24 (ADAS-cog change <math>\geq 4</math> and ADCS-ADL<sub>23</sub> change <math>&lt; 0</math> and ADCS-CGIC <math>&gt; 4</math>)</li><li>• Change from baseline to Week 24 in Mini Mental State Examination (MMSE)</li></ul></li></ul></li></ul>

<ul style="list-style-type: none"> <li>• Change from baseline to Week 24 in EQ-5D utility score</li> <li>• Change from baseline to Week 24 in EQ-5D VAS</li> </ul>
<p><b>Endpoints (continued)</b></p> <ul style="list-style-type: none"> <li>– Endpoints addressing other objectives: <ul style="list-style-type: none"> <li>• PK assessments (for population PK and PK/PD modelling)</li> </ul> </li> <li>• Safety endpoints: <ul style="list-style-type: none"> <li>– adverse events</li> <li>– absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, and ECG parameters</li> <li>– potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values</li> <li>– C-SSRS</li> </ul> </li> </ul>
<p><b>Statistical Methodology</b></p> <p>The following analysis sets will be used to analyse and present the data:</p> <p><i>all-patients-treated set</i> (APTS) – all randomised patients who took at least one dose of double-blind IMP</p> <p><i>full-analysis set</i> (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of ADAS-Cog.</p> <p>The efficacy analyses will be based on the FAS.</p> <ul style="list-style-type: none"> <li>• 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%. The null hypothesis of no difference to placebo in mean change from baseline in ADAS-Cog at Week 24 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 to placebo in mean change from baseline at week 24 for ADCS-ADL 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 has to show statistically significant favourable differences compared to placebo at Week 24.</li> <li>• Analysis of primary endpoint: <p>Changes from baseline of post-baseline assessments at weeks 4, 12, and 24 will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. Analyses will include the fixed, categorical effects of treatment (two doses and placebo), country, visit, treatment-by-visit interaction, MMSE-stratum (&lt;19, ≥19), and MMSE-stratum-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If, unexpectedly, this analysis fails to converge, the following 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 Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary comparisons will be the contrasts between each dose and placebo at the 24 week visit based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between each dose and placebo based on this model will be reported with two-sided symmetric 97.5% confidence intervals and corresponding p-values.</p> <p>Subgroup analyses by MMSE-stratum will be performed on an exploratory basis using the same methodology as that described for the primary analysis excluding MMSE-stratum and MMSE-stratum-by-visit from the model.</p> <p>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.</p> </li> <li>• Analysis of key secondary endpoints: <p>For the key secondary endpoints, the same methodology as that described for the primary analysis 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</p> </li> </ul>

clinical status evaluation, will be used as covariate, however.

Subgroup analyses by MMSE-stratum will be performed on an exploratory basis using the same methodology as that described for the primary analysis excluding MMSE-stratum and MMSE-stratum-by-visit terms from the model.

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.

- Sensitivity analyses of the primary and key secondary endpoints:
  - MMRM analysis including efficacy data collected at the Withdrawal Follow-up Visit and the Drop-out Retrieval Visit for withdrawn patients.
  - Pattern-mixture model in which missing values due to dropout in all treatment arms are imputed using multiple imputations from a model based on the placebo group.<sup>1</sup>
  - MMRM analysis based on patients completing the Week 24 Visit
  - For ADCS-CGIC, a non-linear mixed model for ordinal response will be applied to explore sensitivity to the normal distribution assumption for this variable in the primary analysis

Analysis of secondary endpoints:

- Changes from baseline in total NPI as well as individual NPI items at Week 4, 12, and 24 will be analysed using the same methodology as that described for the primary endpoint
- Changes from baseline in NPI Anxiety item score at Week 4, 12, and 24 in the subset of patients with a score of at least 2 at baseline will be analysed using the same methodology as that described for the primary endpoint
- Emergence of individual NPI items at Week 24 for the subset of patients with a baseline score of 0 for the item 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. The analysis will be based on observed cases with no imputation for missing values.
- The proportion of patients with clinical response 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 without imputation as well as for the whole FAS, imputing a non-response for all patients discontinued prior to Week 24.
- The proportion of patients with clinical worsening 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 without imputation as well as for the whole FAS, imputing a clinical worsening for all patients discontinued prior to Week 24.
- Changes from baseline in MMSE score at Week 24 will be analyzed using an ANCOVA model with treatment, country and MMSE stratum as fixed factors and baseline MMSE score as covariate. The analysis will be based on observed cases with no imputation for missing values.
- 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 described for the primary endpoint

The safety analyses will be based on the APTS.

- Analyses of safety endpoints:

Adverse events, clinical safety laboratory tests, vital signs, C-SSRS, and other safety variables will be summarised using descriptive statistics.

Patient disposition and baseline characteristics will be summarised using descriptive statistics.

**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 or ADCS-CGIC, assuming improvements of 2 points on both ADAS-Cog and ADCS-ADL, and 0.25 on ADCS-CGIC for both doses. The standard deviations (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 ( $N_1$  and  $N_2$ ) and the standard error (SE) of the treatment effect estimate at 24 weeks in 12936A as  $SD=SE/\sqrt{(1/N_1+1/N_2)}$ . 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, 0.38 between ADAS-Cog and ADCS-CGIC, and -0.35 between ADCS-ADL and ADCS-CGIC when adjusting for baseline scores. Multiplicity due to multiple doses and endpoints is adjusted for as explained in the Statistical Methodology. The power has been evaluated by simulation from a multivariate normal distribution with the assumed mean and covariance structure described.

**Ethical Rationale for Study and Study Design**

Patients will be fully informed about the study including the risks and benefits of his/her participation in the study.

All patients participating in this study will receive an active base treatment for AD. The benefit of this design is that no patient will be exposed to risk of not receiving any treatment.

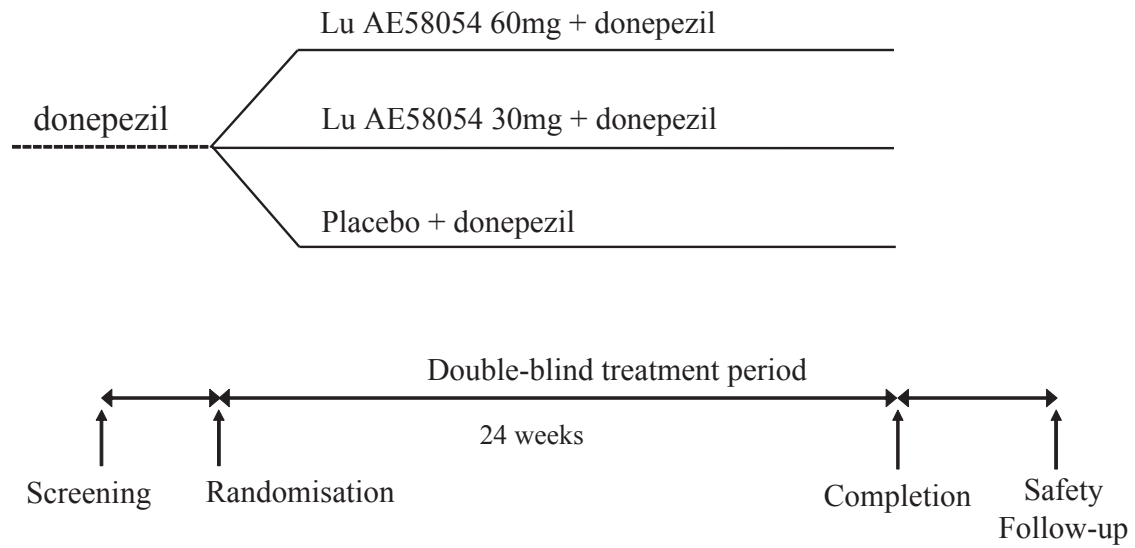
The risks associated with this study are considered adequately elucidated in the non-clinical and clinical studies, well controlled by cautionary measures in the study design, and well balanced with the potential benefits of the treatment.

Since the study will enrol patients with dementia, special attention must be paid to the procedures for informed consent. Ample time must be given for explanation of the consequences of participation in the study. Detailed local procedures on the informed consent process for the patient (or, if applicable, the legal representative and caregiver must fulfil GCP standards, be in accordance with the declaration of Helsinki, and comply with national laws/Ethics Committees requirements.

An independent Data Monitoring Committee (DMC) will monitor the patients' safety according to the *Data Monitoring Committee Charter*.



**Panel 1 Study Design**



**Panel 2 Study Procedures and Assessments**

Visit	Screening	Base- line	Treatment Period				Completion <sup>a</sup> / Withdrawal <sup>b</sup>	Safety/ Withdrawal Follow-up <sup>c</sup>	Drop-out Retrieval <sup>m</sup>
Visit Number	1	2	3	4	5	6	7	8	9
Day/ <sup>d</sup>	-14/-1	0	28/ 4	56/ 8	84/ 12	126/ 18	168/ 24	196/ 28	168/ 24 <sup>n</sup>
Visit Window <sup>e</sup> (days relative to nominal visit)			± 7d	± 7d	± 7d	± 7d	± 7d	+ 7d	± 7d
<b>Screening/Baseline Procedures and Assessments</b>									
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 <sup>f</sup>	√								
Demographics (age, sex, race)	√								
Nicotine and alcohol use	√								
Height	√								
CYP enzyme and ApoE genotyping		√							
Inclusion/exclusion criteria	√	√							
Randomisation		√							
<b>Efficacy Assessments</b>									
ADAS-cog	√	√	√		√		√	√ <sup>g</sup>	√
ADCS-ADL <sub>23</sub>		√	√		√		√	√ <sup>g</sup>	√
ADCS-CGIC		√	√		√		√	√ <sup>g</sup>	√
NPI		√	√		√		√		
<b>Other Assessments</b>									
RUD Lite		√			√		√		
EQ-5D		√			√		√		
Dependence scale		√			√		√		
<b>Safety Assessments</b>									
Adverse events <sup>h</sup>	√	√	√	√	√	√	√	√ <sup>i</sup>	√ <sup>o</sup>
Blood and urine sampling	√	√	√	√	√	√	√		

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

- Patients completing the 24 week Treatment Period may be eligible to enter a 6-month open-label extension study with Lu AE58054 and donepezil.
- This visit should take place as soon as possible after the patient withdraws from the study.
- 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.
- All assessments can be completed over a maximum of two consecutive days, in this case the first day should be considered as the visit day of the study. Note: If a visit takes place over two consecutive days the IMP should be dispensed on the second day, after all assessments have been performed. For visits

- other than the Baseline visit, the visit window must allow for the previously dispensed IMP to last for both visit days.
- e. If the date of a patient visit does not conform to the study plan, subsequent visits should be planned to maintain the visit schedule relative to 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 which are considered as possibly/probably related to IMP by the investigator.
  - p. Only for concomitant medications ongoing at the day of the Drop-out Retrieval Visit.

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## List of Abbreviations and Definitions of Terms

$\gamma$ GT	$\gamma$ -glutamyl transferase
5-HT	serotonin
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale, cognitive subscale
ADCS-ADL23	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
ADL	Activities of Daily Living
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
ApoE	Apolipoprotein E
APRS	all-patients-randomised set
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use (European Union)
CIAS	cognitive impairment associated with schizophrenia (CIAS)
$C_{max}$	Maximum plasma/serum concentration
CNV	copy number variation
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerised tomography
CYP	cytochrome P450 isoenzyme
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DS	Dependence Scale
DSM-IV-TR™	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set

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FDA	United States Food and Drug Administration
GPV	Division of Global Pharmacovigilance, H. Lundbeck A/S
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalised ratio of prothrombin time
IRB	institutional review board
IVRS	interactive voice response system
Lu	Lundbeck
MMRM	mixed model for repeated measurements
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NPI	Neuropsychiatric Inventory
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	specific ECG interval describing atrioventricular conduction
QP	qualified person
QRS	specific ECG interval describing ventricular depolarisation
QT	specific ECG interval describing ventricular depolarisation/repolarisation
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
SD	standard deviation
SE	standard error
SPC	Summary of Product Characteristics
SNP	single-nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TEAE	treatment-emergent adverse event

TID	three times daily
TMF	trial master file
TSH	thyroid stimulating hormone
ULN	upper limit of normal

# 1 Introduction

## 1.1 Background

### 1.1.1 Overview

AD is an irreversible, chronic and progressive neurodegenerative disease which gradually destroys memory, and the ability to learn, reason, make judgments, communicate, and carry out daily activities. In addition, patients may develop symptoms such as inappropriate behaviour and neuropsychological symptoms including aggression, agitation, apathy, depression, and hallucinations. Sleep disturbances are also commonly seen in AD patients.

AD is estimated to affect between 4% to 8% of the population aged above 65 years, and more than 20% of those aged above 85 years. Three disease stages are commonly described in AD: mild, moderate and severe. Today, on average, only half of the patients with AD are correctly diagnosed, most of them in the moderate to severe stages of the disease, and a high percentage of them are not treated with adequate medication.

Lu AE58054 is a selective serotonin receptor 6 (5-HT<sub>6</sub> receptor) antagonist, which is being jointly developed by H. Lundbeck A/S and Otsuka Pharmaceutical Co, Ltd. Lu AE58054 has been shown to improve cognitive performance when administered as adjunctive treatment to the acetylcholinesterase (AChE) inhibitor donepezil in a randomised, double blind, parallel-group, placebo-controlled, fixed-dose study (12936A) conducted in patients with moderate AD. The 5-HT<sub>6</sub> antagonists have pro-cognitive effects in rodents, possibly mediated through a blockade of excitatory input to gamma-aminobutyric acid (GABA)-ergic neurons in the hippocampus and cortex, leading to an indirect enhancement of cholinergic, dopaminergic, and glutamatergic neurotransmission.

The following sections provide an overview of the non-clinical and clinical data currently available for Lu AE58054. Refer to the current version of the *Investigator's Brochure (IB)*<sup>2</sup> for more detailed information.

### 1.1.2 Non-clinical Data

Lu AE58054 is a high affinity antagonist for the 5-HT<sub>6</sub> receptor. Broad profiling of Lu AE58054 in more than 100 additional assays demonstrated medium affinity to the adrenergic  $\alpha$ -1A and  $\alpha$ -1B receptors and to the dopamine D3 receptor. Efficacy profiling showed that Lu AE58054 was an antagonist for the adrenergic  $\alpha$ -1A,  $\alpha$ -1B and dopamine D3 receptors. For all the remaining targets tested, Lu AE58054 demonstrated at least 100-fold selectivity.

Lu AE58054 has been shown to improve performance in multiple rodent cognition tasks. In doses leading to >65% striatal 5-HT<sub>6</sub> receptor occupancy *in vivo*, Lu AE58054 reversed cognitive impairment induced by subchronic phencyclidine in rats. In microdialysis studies, administration of Lu AE58054 alone did not affect extracellular levels of GABA, dopamine,

5-HT or acetylcholine (ACh) in the rat prefrontal cortex, whereas Lu AE58054 (5 mg/kg per os) significantly potentiated donepezil-induced increases in extracellular levels of ACh. This suggests the possibility of synergistic effects when combining Lu AE58054 with acetylcholine esterase inhibitors.

Safety pharmacology and toxicology studies indicate that at clinically relevant exposure levels, Lu AE58054 is well tolerated. Multiple-dose toxicology studies were conducted in rats and monkeys at doses up to 250 mg/kg and 50 mg/kg, respectively. In monkeys, convulsions occurred at high exposure levels. In rats, increased blood clotting time was noticed at high exposure levels.

Exploratory data using human recombinant enzymes indicated that cytochrome P450 isoenzyme (CYP) 3A4 was the major CYP450 enzyme involved in the metabolism of Lu AE58054 with some contribution from CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Lu AE58054 showed inhibitory potential towards CYP2D6 and CYP3A4/5. Furthermore, in an *in vitro* study evaluating the induction potential of Lu AE58054, Lu AE58054 showed little (CYP2B6 and CYP2C8) or no induction potential (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) towards the CYPs investigated.

Further information can be found in the IB.<sup>2</sup>

### 1.1.3 Clinical Data

Six clinical pharmacology studies and three clinical studies with Lu AE58054 have been performed, the three clinical studies were:

- Study 12936A, (phase II, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study exploring the efficacy and safety of Lu AE58054 as adjunctive therapy to donepezil in patients with moderate AD).
- Study CL03 (11974A), (phase II, double-blind, placebo-controlled, dose-ranging parallel-group study in patients with cognitive impairment associated with schizophrenia (CIAS)).
- Study 12450A, (phase II, randomised, double blind, parallel-group, fixed-dose study exploring the efficacy and safety of Lu AE58054 as augmentation therapy to risperidone in patients with schizophrenia).

#### 1.1.3.1 Pharmacokinetics and Pharmacodynamics

In the previous Alzheimer's disease study (12936A), the estimated mean Lu AE58054 maximum concentration ( $C_{max}$ ) and the area under the curve ( $AUC_{0-24h}$ ) following a 30 mg three times daily (TID) dosing regimen were 540 ng/mL and 11700 h\*ng/mL, respectively. Based on the same population PK model, the estimated exposures following the 30 mg once daily and 60 mg once daily dosing regimens will be mean  $C_{max}$  180 ng/mL and 390 ng/mL, and mean  $AUC_{0-24h}$  3170 h\*ng/mL and 6930 h\*ng/mL, respectively.

Donepezil is mainly metabolized by CYP3A4 and to a minor extent by CYP2D6. In study 12936A, the estimated impact of Lu AE58054 CYP2D6 inhibition on donepezil clearance was in agreement with the observed donepezil exposure at Week 4 and onwards

(10% reduction in clearance). In the current study, the impact on donepezil clearance and exposure is expected to be of the same order of magnitude or slightly lower, due to the decreased dose.

Preliminary data from a clinical 5-HT<sub>6</sub> receptor occupancy study show high occupancy following doses of 30 mg once daily and above.

### **1.1.3.2 Efficacy**

Lu AE58054 90 mg/day (30 mg TID) was shown to be effective in improving cognitive function in donepezil-treated patients with moderate AD. This was supported by trends toward improvement in functional and global clinical measures.

### **1.1.3.3 Safety**

Lu AE58054 was safe and generally well tolerated in healthy subjects (young and elderly men and women) following multiple doses up to 300 mg/day with no clinical significant effects on vital signs, clinical laboratory tests or ECG parameters.

In the Phase II study, 12936A, conducted in patients with AD, Lu AE58054 was safe and, with the exception of elevated transaminase values, well tolerated as adjunctive therapy to donepezil in patients with AD at a dose of 90 mg/day (30 mg TID) for 6 months.

In this study, the incidence of treatment-emergent adverse events (TEAEs) was slightly higher in the Lu AE58054 group (66%) than in the placebo group (59%). The most common adverse events, (occurring in >2 patients and with an incidence of more than 4% and with a > 2 times higher incidence in patients treated with Lu AE58054 than in patients treated with placebo), were  $\gamma$ -glutamyltransferase increased, Alanine aminotransferase (ALT) increased, Aspartate aminotransferase (AST) increased, Dizziness, Headache, Aggression, and Vomiting.

The proportion of patients who withdrew due to TEAEs in this study was 15% in the Lu AE58054 group and 7.5% in the placebo group. The difference was almost entirely due to elevated liver enzymes test values reported as TEAEs.

A total of 14 (9.7%) patients in the Lu AE58054 group and 13 (9.8%) patients in the placebo group had one or more serious adverse events (SAEs).

There were more patients in the Lu AE58054 group than in the placebo group who had AST, ALT and/or alkaline phosphatase (AP) values above the upper limit of normal (ULN) at some point during the study. There were no differences between the treatment groups in the incidence of total bilirubin level (TBL) above ULN. A total of 13 patients (all in the Lu AE58054 group) had AST or ALT values that were >2 times ULN. The elevated liver test values were seen around Week 8. For all the 13 patients, the liver test values subsequently decreased towards the reference range. The mechanism behind this increased liver test is currently unknown.



Except for liver tests, the changes from baseline for all clinical safety laboratory tests and ECGs showed, on average, small fluctuations without clinical relevance and with no trends over time or between the treatment groups.

In the two phase II studies conducted in patients with schizophrenia, Lu AE58054 was safe and well tolerated for up to 12 weeks.

Further information on the safety of Lu AE58054 can be found in the IB.<sup>2</sup>

## **1.2 Rationale for the Study**

The rationale for the study is based on the pro-cognitive effects of Lu AE58054 observed in non-clinical and clinical studies. Lu AE58054 has pro-cognitive effects in rodents possibly mediated through a blockade of excitatory input to GABAergic neurons in the hippocampus and cortex, leading to an indirect enhancement of cholinergic, dopaminergic and glutamatergic neurotransmission. Thus, in doses leading to >65% striatal serotonin (5-HT<sub>6</sub>) receptor occupancy in vivo, Lu AE58054 reversed cognitive impairment induced by subchronic phencyclidine in rats. Furthermore, in a recent 24-week phase II clinical trial exploring the efficacy and safety of Lu AE58054 (90 mg/day) as add-on to donepezil (10 mg/day) in patients with moderate Alzheimer's disease, there was better cognitive performance with Lu AE58054 than with placebo throughout the study, with a statistically significant treatment difference in the ADAS-cog total score at Week 24. This was supported by a trend toward improvement in functional and global clinical measures. The rationale of the present study is to confirm these findings with sample sizes adequate to demonstrate significant effect also on key secondary functional or global measures as required by regulatory authorities. The doses in the present study have been selected based on preliminary PET receptor occupancy data (study in reporting).

## **2 Objectives**

### **2.1 Primary Objective**

To establish efficacy of Lu AE58054 as adjunctive therapy to donepezil for symptomatic treatment of patients with mild-moderate Alzheimer's disease.

### **2.2 Secondary Objective**

To investigate the effect of Lu AE58054 as adjunctive therapy to donepezil on neuropsychiatric symptoms in patients with mild-moderate Alzheimer's disease.

### **2.3 Other objectives**

To explore population pharmacokinetics/pharmacodynamics.

## 2.4 Safety objectives

To evaluate the safety and tolerability of Lu AE58054 as adjunctive therapy to donepezil in patients with mild-moderate Alzheimer's disease.

# 3 Study Design

## 3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki*.<sup>3</sup>

This is an interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.

This clinical study will be conducted in compliance with the protocol, *Good Clinical Practice*,<sup>4</sup> and applicable regulatory requirements.

An overview of the study is presented in [Panel 1](#).

The target population for the study is patients with mild to moderate Alzheimer's disease who are on a stable donepezil treatment (base treatment).

The patients will be randomized symmetrically at Visit 2 (Day 0) to one of three treatment groups: Lu AE58054 60mg/day, Lu AE58054 30mg/day or placebo. Randomisation will be stratified by MMSE stratum (12-18, 19-22) based on the Screening Visit assessment of MMSE in order to ensure balance between treatment groups and MMSE strata.

Randomisation will be restricted such that no more than 50% of the randomised patients are in the MMSE 19-22 stratum. This is to mitigate an overrepresentation of patients in the mild segment where recruitment is expected to be easier than in the moderate segment. It ensures adequate representation of patients across the MMSE 12-22 spectrum.

Approximately 930 patients are planned to be randomised: 310 in each treatment group.

A screening period for up to 2 weeks precedes a 24-week double blind treatment period with regular follow-up visits for safety and efficacy assessments. During the treatment period the patients will take the IMP once daily in addition to their base donepezil hydrochloride treatment.

Patients completing the 24 week Treatment Period may be eligible to enter a 6-month open-label extension study with Lu AE58054 and donepezil. Alternatively the patient will be treated according to normal clinical practice.

For patients who do not enter the open-label extension study, the 24-week treatment period is followed by a 4-week safety follow-up period without treatment with IMP.

Patients who discontinue will complete a withdrawal visit at the time of withdrawal, or as soon as possible thereafter. Withdrawn patients, except for those who withdraw consent, will be scheduled for a follow-up visit 4 weeks after the Withdrawal Visit in order to follow-up on safety as well as collecting information on selected efficacy assessments after withdrawal from IMP therapy. Patients who withdraw their consent should still have a safety follow-up visit but the visit must only be recorded in the medical records.

A Drop-out Retrieval Visit is scheduled for all withdrawn patients, except for those who withdraw their consent or discontinue their participation to the study at or after Week 18 (Visit 6). The main purpose of the Drop-out Retrieval Visit is to collect information on selected efficacy assessments after withdrawal from IMP therapy.

A Data Monitoring Committee (DMC) has been established for the study. The DMC ensures that the ethical principles are observed and monitors the safety of the patients (see section 9.6).

### **3.2 Rationale for the Study Design**

This study is designed as a classic placebo-controlled add-on design including two active doses of Lu AE58054. Randomisation and blinding is applied to minimize the risk of bias in the evaluation of the clinical effects of Lu AE58054.

Placebo control is justified since it is an add-on design to standard therapy in this patient group.

The two doses of Lu AE58054 included in the study are both believed to be effective in improving cognition based on prior clinical data and based on target occupancy data.

The primary efficacy endpoint, ADAS-Cog, and the two key secondary endpoints, ADCS-CGIC and ADCS-ADL23, are standard key measures of symptomatic efficacy in clinical studies in mild-moderate AD.

## **4 Study Population**

### **4.1 Numbers of Patients and Sites**

A total of 930 patients will be randomised into this study (310 patients per treatment group) in about 120 sites distributed world wide.

### **4.2 Patient Recruitment**

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

To ensure that only the required number of patients is randomised, the number of screened patients will be monitored closely.

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

### 4.3 Selection Criteria

Inclusion and exclusion criteria:

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

Patients who meet each of the inclusion criteria at the Screening Visit and Baseline Visit (unless otherwise specified) and none of the exclusion criteria at the Screening Visit or Baseline Visit (unless otherwise specified) are eligible to participate in this study.

#### Inclusion Criteria

1. The patient is capable of communicating with the site personnel. The patient and the caregiver are, in the investigator's judgement, proficient in the language in which the psychometric tests will be completed.
2. The patient (and/or if applicable the legal representative if different from the responsible caregiver) and the responsible caregiver are able to read and understand the *Informed Consent Form*.
3. The patient (and/or if applicable the legal representative if different from the responsible caregiver) and the responsible caregiver have signed the *Informed Consent Form*.
4. The patient is willing and able to attend study appointments within the specified time windows.
5. The patient has a knowledgeable and reliable caregiver who will accompany the patient to all clinic visits during the study.
6. The patient is an outpatient consulting a general practitioner or a psychiatrist / neurologist / geriatrician.
7. The patient has probable AD diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (see [Appendix IV](#)).
8. The patient has a Mini Mental State Examination (MMSE) score at screening of at least 12 and no greater than 22.
9. The patient has had a CT or MRI less than 12 months before the Screening Visit (or between screening and baseline) with results consistent with the diagnosis of probable AD.
10. The patient has been treated daily with donepezil for at least 6 months prior to the Screening Visit. The dose must have been stable at 10 mg/day for the last 4 months prior to screening and throughout the screening period.
11. The patient is a man or woman, aged at least 50 years.
12. The patient is ambulatory or ambulatory aided (i.e., walker or cane).
13. The patient's sight and hearing (hearing aid permissible) are, in the investigator's judgement, sufficient for compliance with the study procedures.
14. The patient has a body mass index (BMI)  $\geq 18.5 \text{ kg/m}^2$ .

15. The patient has a normal physical examination at the Screening and Baseline Visits and normal laboratory evaluations, urine tests and ECG results from the Screening Visit, or abnormal findings that are not clinically significant, as judged by the investigator.
16. The patient, if a woman, must have had her last natural menstruation at least  $\geq 24$  months prior to the Screening Visit or have been surgically sterilised prior to the Screening Visit.
17. The patient, if a man, must:
  - a. use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to  $\geq 1$  month after the last dose of IMP, OR
  - b. have been surgically sterilised prior to the Screening Visit

### **Exclusion Criteria**

1. The patient has previously been randomised in this study or in another study with Lu AE58054.
2. The patient has been treated with any investigational product within 60 days or 5 half-lives (whichever is longer) prior to the Screening Visit.
3. The patient has been treated with anti-Amyloid Beta or anti-Tau Protein monoclonal antibodies, or other disease modifying strategies (for active vaccines see Exclusion criterion 4) within one year prior to the Screening Visit.
4. The patient has been treated with an active vaccine targeting Amyloid Beta or Tau Protein.
5. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
6. The patient is under forced treatment.
7. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity to 5-HT<sub>6</sub> receptor antagonists.
8. The patient has evidence of any clinically significant neurodegenerative disease, or other serious neurological disorders other than AD including but not limited to Lewy body dementia, fronto-temporal dementia, Parkinson's disease, Huntington's disease, major cortical stroke, major head trauma, primary or secondary cerebral neoplasia or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning.
9. The patient has a history of seizures, with the exception of febrile seizures in childhood.
10. The patient has a Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) Axis I disorder other than AD including amnesic disorders, delirium, schizophrenia or schizoaffective disorder, bipolar disorder, current major depressive episode, psychosis, panic, post traumatic stress disorder and/or cognitive disorder not otherwise specified. (Note: patients may be included if treated with a stable dose of antidepressants for at least 6 months and not fulfilling DSM-IV-TR criteria for depression at screening).
11. The patient has clinical and radiological findings that fulfil the standards of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la

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Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (see **Error! Reference source not found.**Appendix V).

12. The patient has CT or MRI evidence of hydrocephalus, stroke, a space-occupying lesion, cerebral infection or any clinically significant central nervous system disease other than AD.
13. The patient suffers from mental retardation, organic mental disorders, or mental disorders due to a general medical condition (DSM-IV-TR™ criteria).
14. The patient has a current diagnosis or history of substance abuse (excluding nicotine and caffeine) or alcohol abuse or dependence (DSM-IV-TR™ criteria) within 5 years prior to the Screening Visit.
15. The patient has any other disorder for which the treatment takes priority over treatment of Alzheimer's disease or is likely to interfere with study treatment or impair treatment compliance.
16. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin, that has not been in remission for >5 years prior to the first dose of IMP. Male patients tested positive for prostate-specific antigen (PSA) may be enrolled in the study provided they have been followed up, have been asymptomatic and have had no treatment for prostate cancer.
17. The patient has evidence of clinically significant disease including but not limited to pulmonary, gastrointestinal, renal, hepatic, endocrine or cardiovascular system disease or metabolic disturbance (patients with controlled diabetes, or patients with controlled hypertension, or right bundle branch block, complete or partial, may be included in the study). Patients with pacemakers are eligible provided that they follow a routine check-up with their doctor and are considered stable. As specified in the donepezil summary of product characteristics (SPC) special precaution is needed for patients with asthma, obstructive pulmonary disease, bradycardia, or difficulty in passing urine.
18. The patient takes or has taken disallowed recent or concomitant medication (specified in [Appendix II](#)) or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study.
19. The patient has been treated with a depot neuroleptic within 6 months prior to the Screening Visit.
20. The patient's donepezil therapy is likely to be interrupted or discontinued during the study.
21. The patient is currently receiving memantine or has taken memantine within 2 months prior to the Screening Visit.
22. The patient has clinically significant abnormal vital signs at the Screening Visit.
23. The patient has been tested positive for human immunodeficiency virus (HIV).
24. The patient has been tested positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus / antibodies (anti-HCV), AND has abnormal ALT, AST or bilirubin at the Screening Visit.
25. The patient has been tested positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus /antibodies (anti-HCV) for the first time within the last 6 months prior to the Screening Visit.

- 
26. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:
- a serum creatinine value >1.5 times the upper limit of the reference range, or
  - a serum total bilirubin value >1.5 times the upper limit of the reference range, or
  - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >1.5 times the upper limit of the reference range
27. The patient has an untreated vitamin B12 or folate deficiency that is considered clinically significant, or has clinical and laboratory evidence of untreated thyroid disease. Patients with vitamin B12 or folate deficiency may be enrolled in the study provided they have been on a supplement therapy for >3 months prior to the Screening Visit and are stable. Patients with thyroid disease may be enrolled in the study provided they are stable and euthyroid.
28. The patient has, at the Screening Visit:
- an abnormal ECG that is, in the investigator's opinion, clinically significant, or
  - a heart rate <45 beats per minute, or
  - a PR interval >280 ms, or
  - a QRS interval >150 ms, or
  - a QTcF interval >480 ms (based on the Fridericia correction where  $QTcF = QT/RR^{0.33}$ )
- Patients with a heart rate between 45 and 49 beats per minute or a PR interval between 250 and 280 ms at the Screening Visit must be discussed with the sponsor medical expert before randomisation. The patients can be considered eligible, provided they are stable and there is no safety risk related to their participation in the study as per the investigator's judgement.
29. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
30. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
31. The patient is likely to be placed in a nursing home during the study.
32. The patient has attempted suicide within the last year or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS within the past 12 months).

#### 4.4 Withdrawal Criteria

A patient must be withdrawn from the study if:

- the patient and/or his or her legal representative withdraws his or her consent (defined as a patient and/or his or her legal representative who **explicitly** takes back his or her consent; section 7.4 states how the patient's data will be handled).

- the investigator considers it, for safety and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn.
- any site personnel break the randomisation code for that patient.
- the patient has a serum ALT or AST value >8 times the upper limit of the reference range.\* (Not applicable for the Czech Republic)
- the patient has a serum ALT or AST value >5 times the upper limit of the reference range that is confirmed by testing within 5 days. (Applicable for the Czech Republic only)
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range and a serum total bilirubin value >2 times the upper limit of the reference range.\*
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range and an international normalised ratio of prothrombin time (INR) more than 1.5.\*
- the patient has a serum ALT or AST value >5 times the upper limit of the reference range for >2 weeks.\* (Not applicable for the Czech Republic)
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).\*
- the patient has a QTcF interval >500 ms that is confirmed by an ECG at a visit <2 weeks later.
- the patient attempts suicide or is at significant risk of suicide (either in the opinion of the investigator or defined as a “yes” to suicidal ideation questions 4 or 5 or answering “yes” to suicidal behaviour on the C-SSRS during the study).
- the patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively decided to withdraw from the study, and for whom no alternative contact information is available [this implies that at least two attempts have been made to contact the patient]).

\* in accordance with the FDA "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation".<sup>5</sup>

Patients who withdraw will not be replaced.

## 5 Investigational Medicinal Product

### 5.1 Treatment Regimen

Patients will enter the study at screening on retrospective documented treatment with donepezil for at least 6 months prior to the Screening Visit. The dose of donepezil (10 mg/day) should be stable at least 4 months prior to screening and throughout the screening period.

Randomised patients will be treated open label with donepezil hydrochloride 10 mg/day (base treatment). The IMP will be dispensed as adjunctive treatment to donepezil hydrochloride. The patients will receive two wallet cards at each visit from Visit 2 to Visit 6; one wallet card containing encapsulated IMP, and one containing donepezil hydrochloride tablets. The



patients will be instructed to take 1 capsule of IMP and 1 tablet of donepezil hydrochloride once daily, for oral use. The first dose of IMP and donepezil hydrochloride is to be taken the day after dispensing to the patient. The dose schedules are presented in [Panel 3](#).

Patients in the Lu AE58054 30 mg/day group will receive 30 mg/day of Lu AE58054 as add-on to donepezil hydrochloride 10 mg/day from day 1 to completion of Treatment Period.

Patients in the Lu AE58054 60 mg/day group will receive 60 mg/day of Lu AE58054 as add-on to donepezil hydrochloride 10 mg/day from day 1 to completion of Treatment Period.

Patients in the Placebo group will receive placebo as add-on to donepezil hydrochloride 10 mg/day from day 1 to completion of Treatment Period.

### Panel 3 Dose Schedules

IMP Dispensing Week Day/Visit	Treatment group			Base treatment all patients
	Lu AE58054 30 mg/day	Lu AE58054 60 mg/Day	Placebo	Donepezil hydrochloride 10 mg/day
Week 1 Day 0/Visit 2	30 mg	60 mg	Placebo	10 mg
Week 4 Day 28/Visit 3	30 mg	60 mg	Placebo	10 mg
Week 8 Day 56/Visit 4	30 mg	60 mg	Placebo	10 mg
Week 12 Day 84/Visit 5	30 mg	60 mg	Placebo	10 mg
Week 18 Day 126/Visit 6	30 mg	60 mg	Placebo	10 mg

## 5.2 IMPs, Formulations, and Strengths

The IMPs in this study are:

- Lu AE58054 in encapsulated tablets, 30 mg and 60 mg
- Placebo capsules

Base treatment in this study is:

- Donepezil hydrochloride tablets 10 mg

## 5.3 Manufacturing, Packaging, Labelling, and Storage of IMP

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

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

The IMPs will be identical in appearance and therefore indistinguishable from one another.

The IMP will be provided in 4-week wallet card containing 28+7 capsules and in 6-week wallet cards containing 42+7 capsules to account for the treatment period as per [Panel 2](#) and [Panel 3](#).

The donepezil hydrochloride will be provided in 4-week wallet card containing 28+7 tablets and in 6-week wallet cards containing 42+7 tablets to account for the treatment period as per [Panel 2](#) and [Panel 3](#).

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

No manipulation, repackaging, or relabelling of IMP or donepezil hydrochloride is permitted after QP release by Lundbeck, unless a repackaging/relabelling agreement exists, and the documentation is available to the Department of Clinical Supply Coordination, H. Lundbeck A/S, and, where necessary, new QP releases are made.

The IMP and donepezil hydrochloride will be identified using a unique IMP number.

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

#### **5.4 Method of Assigning Patients to Treatment**

Patients will be assigned a screening number that will be used to identify them throughout the study (the screening number will match that in the *Case Report Form* [CRF]).

An interactive voice response system (IVRS) will be used in this study. When a patient is to be randomised, the investigator will contact the IVRS. The IVRS will randomly allocate the patient to a treatment group during the call and assign the patient a randomisation number, according to specifications from the Department of Biostatistics, H. Lundbeck A/S, and then follow up by fax, e-mail, or the web (depending on availability or preference at the site).

#### **5.5 Dispensing of IMP**

The number of days between two visits must not exceed the number of days for which the patients have been dispensed IMP and donepezil hydrochloride.

Compliance will be assessed by the capsule and tablet counts at each visit. The patients will be asked to return all wallet cards (used and unused) at each visit.

## 5.6 IMP Accountability

The IMPs and donepezil hydrochloride must be tracked using two logs:

- a site-specific log to track the complete inventory (that is, what is shipped between the site and Lundbeck)
- a patient-specific log to track what is dispensed to and returned by the patient.

The investigator and the pharmacist, if applicable, must agree not to dispense any IMP or donepezil hydrochloride to any person, except patients enrolled in the study. The investigator or the pharmacist (if applicable) must maintain an adequate record of the receipt and distribution of the IMPs and donepezil hydrochloride. This log must be available for inspection at any time.

## 5.7 Unblinding Procedures

Division of Global Pharmacovigilance, H. Lundbeck A/S (GPV) and the investigator or pharmacist at the site will have access to the details of the double-blind treatment for each patient. Access to these details will be via IVRS. The DMC may have access to unblinded data as described in the *Data Monitoring Committee Charter*.

The investigator may only break the code if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator should consult the Clinical Research Associate (CRA) before breaking the code, however, the investigator may break the code immediately if he/she feels it is necessary, to ensure the safety of the patient, without prior contact to the CRA. The investigator must record the date, time, and reason for breaking the code on the Completion/Withdrawal Form (this corresponds to the Completion/Withdrawal Visit, as the patient must be immediately with-drawn from the study) and sign the form. If the emergency situation was an adverse event, it must be recorded on an *Adverse Event Report Form*. The CRA must be notified immediately. The IVRS will also capture the date and time of the code break call. Information on the allocated treatment will be provided during the call and by fax or e-mail, depending on availability/preference.

The data for any patient for whom the code is broken at the site will be included in the analyses up to the date and time of code break. From that point on, the patient must be followed up, as appropriate.

## 5.8 Post-study Access to IMP

Patients completing the study may, if eligible, have the option to participate in a 6 month open-label extension study with Lu AE58054 and donepezil.

Patients who do not continue into the open-label extension study will not be provided with Lu AE58054 or donepezil after completing this study. The patients must be treated in accordance with normal clinical practice and may continue on donepezil as per prescription if judged relevant by the investigator.

## 6 Concomitant Medication

Concomitant medication is any medication other than the IMP and donepezil that is taken during the study, including the Screening period.

The concomitant medications that are disallowed during the study are summarised in [Appendix II](#).

Details of all concomitant medication (prescription and over-the-counter) taken < 3 months prior to the Screening Visit must be recorded in the eCRF at the first visit. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit. For any concomitant medication initiated or for which the dose has changed due to a new disorder or worsening of a concurrent disorder, the disorder must be recorded as an adverse event.

## 7 Study Visit Plan

### 7.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in [Panel 2](#). Further details are in section 8.

The Screening Visit should be performed 1 to 14 days prior to the Baseline Visit. The Baseline Visit is scheduled relative to the Screening Visit. Thereafter, all visits during the Treatment Period are scheduled relative to the Baseline Visit. 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 the Baseline Visit. The Safety/Withdrawal Follow-up Visit is scheduled relative to the Completion/Withdrawal Visit.

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.

After completion of IMP treatment (Visit 7), the patient may continue into a 6-month, open-label extension study, if informed consent has been obtained and if eligible as judged by the investigator. Patients who do not continue into the extension study, after the completion visit of this study, must be treated in accordance with normal clinical practice.

### 7.2 Screening Visit (Visit 1)

No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the patient (and/or the legal representative if applicable).

Screening procedures must be performed only after informed consent has been obtained. If needed for selection criteria or patient follow up, it is allowed to use the results of blood

sample analyses, scans, examinations and relevant data collected as part of the routine care of the patients outside study specific procedures or prior to obtaining written informed consent.

### 7.2.1 Re-screening

Re-screening may only be allowed for patients with a *complete* screening visit and who screen fail due to non-treated or undertreated Vitamin B12 deficiency, folate deficiency, thyroid disease (Exclusion Criterion 27) or untreated arterial hypertension (Exclusion Criterion 17) but meet all other eligibility criteria. Authorisation for re-screening must be granted by the sponsor medical expert after thorough review of all data from the original screening visit in the eCRF, and only after the patient in question has been on stable treatment (for the screening failure condition) for at least 3 months and is asymptomatic with normalised laboratory results or blood pressure measurements.

At the re-screening visit, the patient (and/or if applicable the legal representative if different from the responsible caregiver) and the responsible caregiver must sign a new ICF. At re-screening, the patient will be assigned a new screening number. A re-screened patient must complete a full new Screening Visit, and all eligibility criteria must be re-assessed at the re-screening visit.

The following information will also be recorded in the eCRF at re-screening:

- If a patient has previously been screened for the study
- That re-screening has been authorized by the sponsor medical expert
- The screening number that was assigned to the patient at the previous screening visit

For a re-screened patient, none of the data from the original screening visit, where the patient failed to enter the study, will be used in the statistical analysis.

A patient will only be allowed to be re-screened once.

### 7.3 Baseline Visit (Visit 2)

In exceptional cases, the visit interval between the Screening and Baseline Visit may be extended with consent from the Medical Expert, provided the Medical Expert accepts the rationale for the extension.

### Patient Identification Card

Each patient will be provided with a *Patient Identification Card* that states, at a minimum, the name of the IMP, the study number, the patient identification number, the investigator's name, and an emergency telephone number providing 24-hour service.

The *Patient Identification Card* should be returned to the investigator upon completion of the patient's participation in the study.

#### 7.4 Withdrawal Visit and Withdrawal Follow-Up Visit

Patients, who withdraw from the study, prior to completion, will be asked to attend a Withdrawal Visit (Visit 7), if at all possible. The visit must be scheduled as soon as possible after withdrawal.

In addition, patients who withdraw from the study will be asked to return for a Withdrawal Follow-up Visit (Visit 8) 4 weeks after the Withdrawal Visit.

No new information will be collected from patients who withdraw, except information collected in relation to the scheduled Withdrawal and Withdrawal Follow-up Visits (provided the patient does not withdraw consent) or needed for the follow-up of adverse events (section 9.5).

The reason for withdrawal must be recorded on the *Reason for Withdrawal Form* in the CRF.

For patients and/or their legal representatives who withdraw consent:

- if the patient and/or his or her legal representative withdraw(s) consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including this visit will be used
- if the patient and/or his or her legal representative withdraw(s) consent during a telephone conversation, the investigator will ask the patient if he or she will attend a Withdrawal Visit. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including this visit will be used
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment
- if the patient and/or his or her legal representative explicitly request(s) that his or her data not be used from the time of withdrawal of consent onwards, this will be respected
- the Withdrawal Follow-up Visit for patients who withdraw consent must be performed, if at all possible. This visit will be without the efficacy assessments and must only be recorded in the medical records.

#### 7.5 Safety Follow-up Visit/Contact (Visit 8)

The safety follow-up is conducted to capture serious adverse events (SAEs) that occur during the Safety Follow-up Period as well as to follow up on the outcome of adverse events ongoing at the end of the Treatment Period. The safety follow-up will be conducted as a visit to the site. The safety follow-up must be conducted 4 weeks (+ up to 7 days) after the last dose of IMP.

For adverse events that were ongoing at the end of the Treatment Period and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse events still ongoing at the safety follow-up, the stop date must be recorded as “ongoing”. SAEs must be followed until resolution or the outcome is known.

Patients with a clinical safety laboratory test value that was out-of-range at the Completion or Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 4 weeks or until resolution of the abnormality, whichever comes first.

Patients with AST or ALT values > 3 times ULN at the Completion or Withdrawal Visit should be followed until the values normalise or return to the baseline values or a diagnosis has been established (see sections 7.7 and 8.5.3) The results must be recorded in the eCRF until the end of the study (see section 7.7).

The safety follow-up for patients who withdraw consent must be performed, if at all possible; any information obtained will be recorded in the patients' medical records.

## **7.6 Drop-out Retrieval Visit (Visit 9)**

The Drop-out Retrieval Visit is scheduled for all withdrawn patients, except for those who withdraw their consent or discontinue their participation to the study at or after Week 18 (Visit 6). The Drop-out Retrieval Visit must be conducted at the time of the projected Week 24 Visit. This visit will be conducted as a visit to the site. The Drop-out Retrieval Visit will include selected efficacy assessments (ADAS-cog, ADCS-CGIC and ADCS-ADL23). Information about SAEs that occur after the Safety/Withdrawal Follow-up Visit and are considered by the investigator related to the study medication, as well as follow up on the outcome of adverse events ongoing at the Safety/Withdrawal Follow-up Visit, will be collected. For adverse events that were ongoing at the Safety/Withdrawal Follow-up Visit and that resolved prior to Drop-out retrieval visit, the stop date must be recorded. SAEs must be followed until resolution or the outcome is known.

## **7.7 End-of-study Definition**

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

For any increased (abnormal) lab value still present at the time of the last study patient's Visit 8, no follow-up information will be collected within the eCRF. Investigators will however still be required to follow the patients according to normal clinical practice.

For patients who continue in the open-label extension study, the end of study (14861A) is defined as Visit 7 (24 weeks).

## 8 Assessments

### 8.1 Screening and Baseline Procedures and Assessments

#### 8.1.1 Demographics and Other Baseline Characteristics

The following will be subject to assessment after the Informed Consent Form has been signed:

- Demographics (age, sex, race), height, weight, BMI
- Social (including years of education), medical, neurological (including AD history stating onset, duration, severity) and psychiatric history
- Nicotine and alcohol use
- Physical examination (appearance, extremities, skin, head, neck, ears, nose, throat, lungs, chest, heart, abdomen and musculoskeletal system)
- Neurological examination (cranial nerves, motor system, sensory system, reflexes, cerebellar function and gait)
- Clinical safety laboratory tests (as listed in [Panel 4](#))
- Recent and concomitant medication
- CT or MRI can be done at the Screening Visit or between the Screening Visit and Baseline Visit if not performed within the last 12 months. Results must be available before randomisation. No central reading will be done.
- CYP enzyme and Apolipoprotein E (ApoE) genotyping
- Exploratory biomarker assessments

Height and weight without shoes will be measured.

#### 8.1.2 Diagnostic and Screening Assessments

NINCDS-ADRDA criteria for AD, MMSE and NINDS-AIREN are the diagnostic and screening assessment tools to be used when assessing patient eligibility.

At the Screening visit, the MMSE should be performed prior to any of the other assessments, including ADAS-cog.

The NINCDS-ADRDA criteria specify eight cognitive domains that may be impaired in AD: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving, and functional abilities. For probable Alzheimer's disease, dementia has to have been established by clinical and neuropsychological examination. Cognitive impairments have to be progressive and be present in two or more areas of cognition. The onset of deficits has to have been between the ages of 40 and 90 years and there must be an absence of other diseases capable of producing a dementia syndrome.<sup>6</sup>



The NINDS-AIREN<sup>7</sup> criteria are clinical criteria for vascular dementia used to identify patients with vascular dementia that should be excluded.

### **8.1.2.1 Mini Mental State Exam (MMSE)**

The MMSE<sup>8</sup> is a test designed to assess the cognitive aspects of mental function. The test assesses 11 cognitive areas: orientation (items for time and place), memory (items for registration and recall), attention and calculation, language (items for naming, repetition, comprehension, reading and writing) and visual construction (item for drawing). The items are administered in the order listed and rated immediately. The score for each item is dichotomous (1 = response is correct, 0 = response is incorrect). The total score of the items ranges from 0 to 30, where the higher scores indicate lower impairment of cognitive function. An experienced clinician can use the MMSE after a short training session. It takes approximately 10 minutes to administer and score the MMSE.

The MMSE will be administered in the local language. Only scales provided by Lundbeck that have been validated in the language to which they have been translated will be used in this study.

External quality oversight methods (video and worksheet review) will be used to verify the accuracy of the MMSE scoring. At the Screening Visit, this will include video monitoring of the MMSE which should be externally reviewed and the total score confirmed before randomisation of the patient. If technical issues prevent external review, randomisation will be based solely on worksheet review. If patients object to being video recorded, the camera can focus only on the rater administering the test. The videos will be uploaded to a server with limited and controlled access. The videos will be destroyed at the end of the study with Lundbeck's agreement. Video monitoring and review will be performed on behalf of Lundbeck by ePharmaSolutions.

Detailed instructions on how to administer and score the MMSE will be provided to the site in a Rater Guideline.

### **8.1.3 CYP enzyme and ApoE genotyping**

A (4 mL) venous blood sample for genotyping will be collected in an EDTA tube at the Baseline Visit. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

Based on known relation to Alzheimer's disease the following genetic variation for apolipoprotein E will be determined:

ApoE: rs429358 (E4) and rs7412 (E3)

Based on in vitro examination of elimination routes for Lu AE58054, the following genetic variation for cytochrome P450 drug metabolising enzymes will be determined:

CYP2C19: alleles \*2,\*3 and \*17

CYP2D6: alleles \*3, \*4, \*5, \*6, \*9, \*10, \*17, \*29,\*41 and \*1xN, \*2xN (gene duplication)

For each individual sample, the genotyping laboratory must report single nucleotide polymorphisms (SNPs) results, conclusive genotype and inferred phenotype, if relevant.

The blood samples will be analysed at the central laboratory by means of a validated analysis method. The samples will be destroyed after completion of the analysis.

Genotyping results will be used for explorative interpretation of the efficacy and pharmacokinetic results, respectively.

## **8.2 Efficacy Assessments**

### **8.2.1 Use of the Efficacy Assessments**

The following assessments will be used:

- ADAS-Cog – assessing cognitive impairment
- ADCS-CGIC – blinded assessment of clinical global impression of change
- ADCS-ADL – assessing activities of daily living
- NPI – assessing neuropsychiatric symptoms

The efficacy assessments will be administered in the local language. Only scales provided by Lundbeck that have been validated in the language to which they have been translated will be used in this study.

Detailed instructions on how to administer and score the efficacy assessments will be provided to the site in a Rater Guideline.

At all visits (other than Screening Visit), the ADAS-Cog should preferably be the first efficacy assessment performed, and the same order of assessments should be used per patient.

#### **8.2.1.1 Alzheimer's Disease Assessment Scale – cognitive sub-scale (ADAS-Cog)**

The ADAS-Cog<sup>9</sup> is a test designed to assess cognitive symptoms associated with Alzheimer's disease and is devised to be sensitive to change. The ADAS-Cog consists of 11 items to 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 total score of the 11 items ranges from 0 to 70, with a lower score indicating lower cognitive impairment.

An experienced clinician can administer the ADAS-Cog after a short training session. It takes 20-35 minutes to administer and rate the ADAS-Cog.

External quality oversight methods (video and worksheet monitoring) will be used to verify the accuracy of the ADAS-Cog administration. The videos will be uploaded to a server with

limited and controlled access. The videos will be destroyed at the end of the study with Lundbeck's agreement. Video monitoring and review will be performed on behalf of Lundbeck by ePharmaSolutions.

### **8.2.1.2 Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC)**

The ADCS-CGIC<sup>10</sup> is a semi-structured interview designed to assess clinically relevant changes in patients with Alzheimer's disease. The ADCS-CGIC interview is guided by probes covering cognition, behaviour, and social and daily functioning. The severity of the symptoms are based on answers from both the patient and the caregiver. A global clinical judgement of severity at baseline is used as a reference for subsequent visit change scores and is rated from 1 (normal, not at all ill) to 7 (among the most extremely ill patients). At subsequent visits, a global impression of change from 1 (marked improvement) to 7 (marked worsening) is rated in comparison to the baseline reference.

The ADCS-CGIC can be administered by an experienced clinician after a short training session. It takes approximately 30 to 45 minutes to administer the ADCS-CGIC.

The ADCS-CGIC rater must be blinded to all other efficacy and safety assessments, with the exception of the baseline (Visit 2) rating, when the raters may have access to all information about the patient. Sites should make all efforts possible to ensure the blinding of the CGIC rater is respected. In case the ADCS-CGIC rater administers other scales to other patient(s), the rater must keep an up to date listing with the patient(s) identification (screening number) and the corresponding scales administered. This listing must be available in the I-TMF throughout the study.

External quality oversight methods (worksheet review) will be used to verify the accuracy of the ADCS-CGIC scoring.

### **8.2.1.3 Alzheimer's Disease Co-operative Society – Activities of Daily Living (ADCS-ADL) Inventory**

The ADCS-ADL<sub>23</sub><sup>11</sup> is a standardised, clinician-rated inventory designed to assess activities of daily living (ADL) in patients with Alzheimer's disease over a defined period. The ADCS-ADL<sub>23</sub> consists of 23-items and is conducted with a caregiver or informant who is in close contact with the patient. Each item in the ADCS-ADL<sub>23</sub> (for example, eating, walking, bathing) comprises a series of hierarchical sub-questions, ranging from the highest level of independent performance to a complete loss for each ADL. The total score of the 23 items ranges from 0 to 78, with higher scores indicating less impairment.

The ADCS-ADL<sub>23</sub> can be administered by an experienced clinician after a short training session. It takes 30 to 45 minutes to administer and rate the ADCS-ADL<sub>23</sub>.

#### **8.2.1.4 Neuropsychiatric Inventory (NPI)**

The NPI<sup>12,13,14</sup> is a 12-item structured interview with a caregiver designed to assess behavioural disturbances in patients with dementia. The NPI comprises 10 behavioural and 2 neurovegetative items. Each item consists of a screening question and several sub-questions which are rated no (not present) or yes (present). Each item is then rated for frequency (a 4-point scale from 1 [occasionally] to 4 [very frequently]), severity (a 3-point scale from 1 [mild] to 3 [marked]), and caregiver distress (a 6-point scale from 0 [not at all] to 5 [very severely or extremely]). The total score<sub>12items</sub> of the frequency and severity ratings range from 0 to 144 and the total score<sub>12items</sub> of caregiver distress ranges from 0 to 60.

An experienced clinician can use the NPI after a short training session. It takes approximately 30 minutes to administer and score the NPI.

#### **8.2.2 Rater Qualification**

The ADAS-Cog and MMSE should only be administered by a rater having adequate experience with patients with Alzheimer's disease and administration of cognitive tests. The rater should be a neurologist, geriatrician, psychiatrist, (neuro-)psychologist involved in clinical practice. Any exceptions (including experienced study nurses) must be discussed and approved by a Lundbeck Scales Manager.

The ADCS-CGIC, ADCS-ADL and NPI should only be administered by a rater having adequate experience with patients with Alzheimer's disease and administration of (semi-)structured interviews. The rater should be a neurologist, geriatrician, psychiatrist, (neuro-)psychologist involved in clinical practice. Any exceptions (including experienced study nurses) must be discussed and approved by a Lundbeck Scales Manager.

Only raters who qualify on study-specific Rater Certification Programme will be authorised to rate in the study. Documentation of training and certification will be delivered to raters for archiving in the investigator trial master file (TMF). No patient must be rated before the documentation has been delivered.

For each individual patient, the same certified rater should preferably rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study. In case of temporary change of rater, the primary rater should take over rating the patient as soon as returned to the site. A hand-over between primary rater and back-up rater should be documented.

Rater training and certification will be performed by ePharmaSolutions.

External data monitoring will be performed by ePharmaSolutions.

Lundbeck reserves the right to use external quality oversight methods to verify correct administration and scoring. This includes video monitoring of the Screening Visit MMSE and ADAS-Cog assessments and worksheet review of MMSE and ADAS-Cog and ADCS-CGIC assessments.

### 8.3 Pharmacoeconomic Assessments

The following pharmacoeconomic assessments will be used:

- EQ-5D-3L (by proxy) – assessing quality of life
- RUD Lite – assessing healthcare resource utilisation
- Dependence scale – assessing dependence

#### 8.3.1 EQ-5D-3L (proxy)

The EQ-5D-3L will be completed by the patient's caregiver as a proxy for the patient.

The EQ-5D-3L<sup>15</sup> is a patient-reported assessment designed to measure the patient's well-being. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each descriptive item is rated on a 3-point index ranging from 1 (no problems) to 3 (extreme problems) and a single summary index (from 0 to 1) can be calculated. The VAS ranges from 0 (*worst imaginable health state*) to 100 (*best imaginable health state*). It takes approximately 5 minutes to complete the EQ-5D-3L.

#### 8.3.2 Resource Utilisation in Dementia (RUD) – Lite

The RUD Lite<sup>16</sup> is a caregiver questionnaire designed to assess resources required for patients with dementia. The RUD Lite consists of two sections: one about the caregiver (covering caregiver demographics, time spent by the caregiver on assisting the patient with personal and instrumental activities of daily living and supervision, and caregiver work status); and one about the patient (covering the patient's accommodation status and healthcare resource utilisation). The RUD Lite can be administered by study-site staff. It takes approximately 15 minutes to complete the RUD Lite.

#### 8.3.3 Dependence Scale (DS)

The DS<sup>17</sup> is a clinician-rated scale designed to measure dependence as a health outcome measure in Alzheimer's disease. The DS consists of 13 questions on social and occupational functioning. The clinician interviews the patient's caregiver (who lives with or is well informed about the patient's day to day activities). Two questions are rated by frequency (*no*, *occasionally*, *frequently*) and the remaining 11 questions have *yes* or *no* responses. The answers are used to derive a dependence level from 0 (*no dependence*) to 5 (*complete dependence*). The DS can be rated by a clinician after a short training session. It takes approximately 15 minutes to complete the scale.

The DS should be completed following the ADCS-ADL by the same rater.

## 8.4 Pharmacokinetic/Pharmacodynamic Assessments

Venous (2 mL) blood samples for IMP analysis will be collected in EDTA tubes. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed for Lu AE58054 and relevant metabolites as well as for donepezil using analysis methods validated according to the FDA Guidance for Industry and the EMA Guideline on bioanalytical method validation.<sup>18,19</sup> A bioanalytical protocol will be prepared by Lundbeck prior to initiation of the bioanalysis of the blood samples.

Actual time, date of blood sampling and dosing history (that is, dose, date and time of last administration) of IMP and donepezil hydrochloride will be recorded in the eCRF.

If other metabolites are identified and considered significant, these may be included in an exploratory analysis.

## 8.5 Safety Assessments

### 8.5.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS<sup>20</sup> is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study. The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of ideation, and 4 questions addressing suicidal behaviour. Different versions of the scale are available: in this study the “Baseline” version (lifetime assessment) will be used at the Screening Visit and the “Since last visit” version at all subsequent visits. An experienced clinician can use the C-SSRS after a short training session. It takes approximately 5 minutes to administer and rate the C-SSRS.

The C-SSRS should be rated by a neurologist, geriatrician, psychiatrist or (neuro-) psychologist involved in clinical practice. Any exceptions must be discussed and approved by a Lundbeck Scales Manager.

A C-SSRS training session will be organised prior to the start of the study. Documentation of training and certification will be delivered to raters for archiving in the investigator TMF. No patient must be rated before the documentation has been delivered.

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

### 8.5.2 Adverse Events

Patients will be asked a non-leading question (such as, “how do you feel?”) at each visit, starting at baseline. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by

the patient will be recorded, and the investigator will assess the seriousness and the intensity of the adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See chapter 9 for further information on adverse events.

### 8.5.3 Clinical Safety Laboratory Tests

The clinical laboratory tests are listed in Panel 4 and will be taken at the visits indicated in Panel 2.

#### Panel 4 Clinical Safety Laboratory Tests

<b>Haematology</b> B-haemoglobin B-total leucocyte count B-neutrophils (% of total leucocytes) B-eosinophils (% of total leucocytes) B-basophils (% of total leucocytes) B-lymphocytes (% of total leucocytes) B-monocytes (% of total leucocytes) B-thrombocyte count	<b>Liver<sup>a</sup></b> S-total bilirubin S – conjugated bilirubin (only if total bilirubin is high abnormal) S-alkaline phosphatase (AP) S-alanine aminotransferase (ALT) S-aspartate aminotransferase (AST) S-γ-glutamyl transferase (γGT)	<b>Kidney<sup>a</sup></b> S-creatinine S-urea nitrogen	<b>Infection</b> S-C-reactive protein (CRP)
	<b>Lipids<sup>a</sup></b> S-cholesterol total S-triglycerides (non-fasting)	<b>Electrolytes<sup>a</sup></b> S-sodium S-potassium S-hydrogencarbonation (HCO <sub>3</sub> <sup>-</sup> ) S-calcium (total)	<b>Urine<sup>c</sup></b> U-protein U-glucose U-occult blood U-ketones
		<b>Nutritional<sup>a</sup></b> S-albumin S-glucose (non-fasting) S-B12 <sup>b</sup> S-Folate <sup>b</sup>	<b>Coagulation</b> P-INR aPTT
		<b>Endocrinology<sup>b</sup></b> S-TSH S-T3 (if TSH abnormal) S-T4 (if TSH abnormal)	

B – blood; S – serum; U – urine; P - plasma

a Clinical chemistry

- b Performed at the Screening Visit only
- c Microscopic examination (leucocytes, erythrocytes, and casts) will be performed only if any of the urine evaluations are abnormal.

The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed at the central laboratory specified in [Appendix III](#).

Urine samples will be collected and they will be analysed at the central laboratory.

The investigator must review (initial and date) the results of the clinical safety laboratory tests as soon as possible after receipt of those results. Out-of-range values must be interpreted by the investigator with a comment of “not clinically significant” or “clinically significant” with a comment concerning the planned follow-up. Tests for clinically significant out-of-range values must be repeated, or an appropriate clinical follow-up must be arranged by the investigator and documented on the laboratory report, until the value has stabilised or until the value has returned to a clinically acceptable value (regardless of relationship to IMP). Any value that was out-of-range at the Completion/Withdrawal Visit and was judged clinically significant must be followed according to accepted medical standards for up to 4 weeks or until resolution of the abnormality, whichever comes first. Any out-of-range values, except for AST or ALT, followed after the last protocol-specified contact with the patient will be documented in the patient’s medical records. Patients with AST or ALT values >3 times ULN at the Completion or Withdrawal Visit should be followed until the values normalise or return to the baseline values or a diagnosis has been established (see sections [7.7](#) and [8.5.3](#)). The results must be recorded in the eCRF until the end of the study (see section [7.7](#)).

Patients with repeat testing (within 48-72 h) showing AST/ALT >3 times ULN should follow “close monitoring” with:

- Repeating liver enzymes (AST, ALT, AP,  $\gamma$ GT) and serum bilirubin 2-3 times weekly. Frequency of re-testing can be decreased to once a week or less if abnormalities stabilise, or the patient is withdrawn and the patient is asymptomatic. The samples for the follow-up laboratory tests should preferably be taken at site and processed at the central laboratory. If this is not at all possible, local laboratories are accepted.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (for example INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.



Clinically significant out-of-range values must be recorded as an adverse event on an *Adverse Event Report Form*.

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

#### **8.5.4 Vital Signs**

Please refer to [Panel 2](#) for time-points of assessments.

Blood pressure and pulse rate will be measured using a standard digital meter after the patient has rested for at least 5 minutes in a supine position. The patient must then be instructed to change from a supine to a standing position in a manner consistent with his/her normal routines and that includes passing through a sitting position before assuming an upright position. Blood pressure and pulse rate will be measured after the patient has been standing for at least 1 minute but no longer than 5 minutes.

Measurements are to be obtained for a specific patient in the same manner (preferably from the same arm) throughout the study. Care should be taken to avoid stressful stimuli such as blood sampling immediately prior to measurements.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Report Form*.

#### **8.5.5 Weight**

Patients will be weighed wearing light clothing and no shoes. A similar amount of clothing must be worn on each occasion.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Report Form*.

#### **8.5.6 Electrocardiograms (ECGs)**

A standard 12-lead electronic ECG (eECG) will be performed using digital ECG recording equipment provided to the investigator or, upon agreement, to an external cardiology centre. The eECGs will be transferred digitally to a central ECG laboratory for evaluation. The investigator will be provided with the results and a cardiological interpretation of the ECG from the central ECG laboratory.

Twelve-lead ECGs will be recorded at the Screening Visit and the visits specified in [Panel 2](#). ECG recordings will be obtained after the patient has been supine and at rest for at least 5 minutes. The ECG will be repeated in case of the central reader judge it as unreadable.

A manual covering all relevant procedures for ECG recording will be provided to the sites.

The investigator has the final decision on the clinical significance of ECG abnormalities other than those described in: Exclusion criterion 28 or withdrawal criterion: “the patient has a QTcF interval >500 ms that is confirmed by an ECG at a visit <2 weeks later.

Abnormalities of clinical significance must be recorded as an adverse event on an Adverse Event Report Form.

### **8.5.7 Physical and Neurological Examinations**

The physical examination (including height at the Screening Visit only) must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen (including the renal regions) and musculoskeletal system and must be performed by a physician. The investigator may appoint a designee to be primarily responsible for performing the physical examination. If the appointed designee is to perform the physical examination, he/she must be permitted to do so according to local regulations and the investigator must take responsibility for reviewing the findings. Whenever possible, the same individual should perform all the physical examinations.

The neurological examination comprises an evaluation of cranial nerves, motor system, sensory system, reflexes, cerebellar function and gait and must be performed by a physician.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Report Form*.

## **8.6 Exploratory Biomarker Assessments**

### **8.6.1 General Considerations**

The search for disease or drug response biomarkers may be approached using different methods. These include characterization of gene variants (DNA) or blood levels of messenger ribonucleic acid (mRNA), endogenous metabolites or proteins (metabolomic/proteomic) involved in biological processes implicated in AD. The three approaches complement each other, as they are in effect looking at the same biological processes, albeit at different stages of the gene-to-phenotype cascade.

For this reason blood samples beyond CYP enzyme and ApoE genotyping will be collected for possible future explorative biomarker research and the explorative analysis is not specifically related to this study.

In order to find novel biomarkers not previously associated with the disease, a hypothesis generating approach (genome wide scans using micro arrays) may be used for the gene expression profiling and genotyping.

Although the exploratory biomarker analyses may help to increase our understanding of the aetiology of Alzheimer’s disease and the molecular basis of the drug response, the efforts described in this protocol are strictly research based. Thus, as the complex interactions

between genes and disease are currently not characterised to a level that translates to a meaningful clinical advantage, individual results from the exploratory biomarker analyses will not be given to the patients. For the same reasons, individual results will not be added to the patients' medical records.

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

As blood sampling for exploratory genomics (mRNA) and metabolomics is an integrated part of the study, the main *Patient Information Sheet* covers these analyses. Conversely, sampling for genetic (DNA) biomarker analysis is optional and a separate *Patient Information Sheet* covers this analysis.

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

The blood samples genomics and metabolomics will be single-coded using the patient's screening number. The blood samples for genetic biomarker analysis will be double-coded as described in EMA's position paper on pharmacogenetic terminology<sup>21</sup> to ensure patient privacy protection.

One code key will be stored at the site and the other at the Department of Biostatistics, H. Lundbeck A/S. To link a DNA sample to a specific patient, both code keys are needed. The two code keys will only be used in combination to link a patient to a DNA sample if the patient and/or his or her legal representative withdraw(s) his or her consent and requests that the DNA sample be destroyed.

### **8.6.2 Blood Sampling for Gene Expression Profiling (mRNA)**

A venous blood sample will be collected in (2 x 2.5 mL) PAXgene RNA tubes at the Baseline Visit.

The maximum volume of blood to be collected during the study for this purpose will be 5 mL.

The samples for gene expression profiling will be shipped to Lundbeck Research USA for sample preparation and analysis. The analysis may be performed by a Contract Research Organisation (CRO) or by a bona fide research collaborator.

### **8.6.3 Blood Sampling for Metabolomic/Proteomic Biomarkers**

A venous blood samples will be collected in an (10 mL) EDTA tube at the Baseline Visit.

The maximum volume of blood to be collected during the study for this purpose will be 10 mL.

The samples for Metabolomic/Proteomic will be shipped to Lundbeck Research USA for sample storage. The analysis may be performed by a Contract Research Organisation (CRO) or by a bona fide research collaborator.

#### **8.6.4 Blood Sampling for Pharmacogenetics (DNA)**

It is optional for the patient to donate a blood sample for exploratory pharmacogenetic analysis.

A venous (10 mL) blood sample will be collected in an EDTA tube for subsequent DNA extraction.

Blood tubes will be shipped on dry ice to the central laboratory, where DNA will be extracted and retained. DNA aliquots will be shipped to Lundbeck Research USA for storage.

The genetic variants to be analysed may include single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). The analytical methods may be polymerase chain reaction (PCR), qPCR (quantitative PCR), sequencing, or whole genome scans on microarrays. The analysis may be performed by a Contract Research Organisation (CRO) or by a bona fide research collaborator.

#### **8.7 Total Volume of Blood Drawn and Destruction of Blood**

The total volume of blood drawn from each patient will be approximately 105 mL (including the optional pharmacogenetic blood sample) during the study.

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

The blood samples and any derived material for exploratory biomarker assessments will be destroyed  $\leq 10$  years after the end of the study.

#### **8.8 Patient Compliance**

Responsible study personnel will dispense wallet cards containing donepezil hydrochloride and Lu AE58054 or placebo. Accountability and compliance verification should be documented in the patient's source documents and verified by the CRA during monitoring. Patients must be counselled at each visit on the importance of taking the IMP and donepezil hydrochloride as directed.

## 9 Adverse Events

### 9.1 Definitions

#### 9.1.1 Adverse Event Definitions<sup>22</sup>

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

An adverse event can therefore be any unfavourable and unintended sign (for example, an out-of-range laboratory value), symptom, or disease temporally associated with the use of a pharmaceutical product, regardless of whether it is considered related to the pharmaceutical product.

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

*Serious adverse event (SAE)* – is any adverse event that:

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

Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasia, convulsions that do not result in hospitalisation, development of drug dependency, and drug abuse.

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

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

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

*Suspected unexpected serious adverse reaction (SUSAR)* – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the *Investigator's Brochure*<sup>2</sup> and related to an investigational product by either the investigator or the sponsor.

*Overdose* – is a dose taken by a patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) has, at a minimum, to be recorded as a non-serious adverse event. The nature of the overdose must be clarified (for example, medication error, accidental overdose, or intentional overdose).

## 9.1.2 Adverse Event Assessment Definitions

### Assessment of Intensity

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

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

### Assessment of Causality

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

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

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

For pre-treatment adverse events, a causality assessment concerning study procedures should be provided.

## Assessment of Outcome

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

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

## 9.2 Pregnancy

If the partner of a man participating in the study becomes pregnant, the outcome of the pregnancy should be followed, if the partner agrees.

## 9.3 Recording Adverse Events

Adverse events (including pre-treatment adverse events) must be recorded on an *Adverse Event Report Form*. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours); intensity; causal relationship to IMP; action taken; and outcome. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose).

If the adverse event is *serious*, this must be indicated on the *Adverse Event Report Form*. Furthermore, the investigator must fill out a *Serious Adverse Event Report Form* and report the SAE to Lundbeck immediately after becoming aware of it (section 9.4).

Adverse events, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

## 9.4 Reporting Serious Adverse Events

The investigator must report SAEs to Lundbeck immediately, and under no circumstances should this exceed 24 hours after becoming aware of them, by completing a *Serious Adverse Event eCRF Form* in Rave®.

The initial report must contain as much information as possible and, if more information about the patient’s condition becomes available, the eCRF must be updated with the additional information.

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

Global Pharmacovigilance (GPV)  
Fax: +45 36 30 99 67  
e-mail: [safety@lundbeck.com](mailto:safety@lundbeck.com)

The initial report must contain as much information as possible and, if more information about the patient's condition becomes available, a follow-up report with the additional information must be submitted using the same procedure as that for the initial report.

The signed (original) *Serious Adverse Event Report Form* must be collected by the CRA and filed in the sponsor TMF.

Lundbeck will assume responsibility for reporting SUSARs to the authorities in accordance with local regulations. In those Member States of the European Union that have implemented the European Union *Clinical Trials Directive*<sup>23</sup> and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ethics committees.

Lundbeck will assess expectedness and inform the investigators about SUSARs via the monthly, blinded line listings or in accordance with local requirements. In the countries where unblinded expedited reporting is not required, it is thereafter the investigator's responsibility to report blinded SUSARs to the ethics committee, unless otherwise stated and documented by the ethics committee.

## 9.5 Treatment and Follow-up of Adverse Events

Patients with adverse events that occur during the study must be treated according to usual clinical practice at the discretion of the investigator.

Non-serious adverse events must be followed up until resolution or the safety follow-up assessment, whichever comes first. At the Safety Follow-up Visit, information on new SAEs, if any, and stop dates for previously reported adverse events must be recorded.

For follow-up of adverse events of safety laboratory test see [8.5.3](#).

It is the responsibility of the investigator to follow up on all SAEs until the patient has recovered, stabilised, or recovered with sequelae, and to report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultations.

SAEs that are spontaneously reported by a patient to the investigator after the safety follow-up assessment must be handled in the same manner as SAEs that occur during the study. These SAEs will be captured in the GPV database.



## 9.6 Study Monitoring Committees

### Data Monitoring Committee

The Data Monitoring Committee (DMC) consists of specialists within relevant therapeutic areas. The DMC ensures that the ethical principles are observed and monitors the safety of the patients. To fulfil its responsibilities, the DMC may have access to unblinded data as described in the *Data Monitoring Committee Charter*. The DMC will be informed to what extent the data and analyses provided to them have been quality controlled. Members of the DMC are not involved in other study-related tasks. The DMC procedures are described in the *Data Monitoring Committee Charter*.

## 10 Data Handling and Record Keeping

### 10.1 Data Collection

#### 10.1.1 Electronic Case Report Forms (eCRFs)

eCRFs will be used to collect all the data related to the study, except the external data described in section 10.1.3.

The eCRFs use third party software (Medidata Rave®) to capture data via an on-line system on a computer. Data related to the study will be recorded electronically into a central database over encrypted lines, and all entries and modifications to the data will be logged in an audit trail. Access to the system will only be granted after appropriate and documented training. Written instructions for using the system will be provided along with the training.

Electronic signatures will be used where signatures are required on pages and/or visits. Automated data entry checks will be implemented where appropriate; other data will be reviewed and evaluated for accuracy by the CRA. All entries, corrections, and changes must be made by the investigator or delegate.

#### 10.1.2 Patient Binders

##### 10.1.2.1 Use of Patient Binders

Lundbeck will provide a *Patient Binder* for each patient. The *Patient Binder* contains different types of source documents, organised by visit and type. A ballpoint pen with waterproof ink must be used to enter information in the *Patient Binder*.

Data from the source documents should be recorded in the eCRF within 3 days of the patient visit.

### **10.1.2.2 Rating Scales and Caregiver Outcome**

The Patient Binder contains paper versions of the scales and caregiver outcomes. They will be completed by the rater(s) and caregiver, respectively. The data will be transcribed to the Scoring Sheets in the eCRF by the investigator or a delegate.

The rater(s) must verify that all data entries in the Scale Section are accurate and correct by signing and dating the relevant pages.

Caregivers' responses cannot be corrected by the site staff.

### **10.1.2.3 Other Assessments and Forms**

This section of the Patient Binder contains non-scale worksheets (for example, safety assessments, IMP accountability). It also contains folders for storing ECG traces and laboratory reports.

### **10.1.2.4 Serious Adverse Event Fallback Forms**

*Serious Adverse Event Fallback Forms* must be used when the eCRF cannot be accessed.

## **10.1.3 External Data**

### **10.1.3.1 Transfer of External Data**

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

The clinical safety laboratory results and the results of the analysis of ApoE and CYP will be transferred to Lundbeck by Quintiles Laboratories.

The ECG results will be transferred to Lundbeck by Quintiles Cardiac Safety Services.

### **10.1.4 Data Lock**

When the study data have been declared to be complete and accurate, the data will be locked in accordance with Lundbeck's standard operating procedures.

## **10.2 Retention of Study Documents at the Site**

### **10.2.1 eCRF Data**

After site closure, the investigator will no longer have read access to the eCRF. Instead, each site will be provided with a CD-ROM containing all data related to the site (including eCRF data, queries, and the audit trail). As a CD-ROM is not considered a durable medium and may

therefore not be readable for the full retention period of 15 years, it is possible for the investigator to request a new CD-ROM with all data related to the site from Lundbeck.

### **10.2.2 Other Study Documents**

The investigator must keep the investigator's set of documents in the investigator TMF for at least 15 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever has the most stringent requirements.

The investigator will be requested to store the investigator TMF in a sealed archive box at an off-site storage facility to ensure safe storage and easy retrieval of the study documents for the entire retention period.

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

Lundbeck will notify the investigator in writing when the required storage period has expired and when the documents may be destroyed according to regulations.

## **11 Monitoring Procedures**

Prior to including patients in the study, the investigator must sign a source data agreement that identifies the source documents (original documents, data, and records) at the site.

During the study, the CRA will visit the study site to ensure that the protocol is being adhered to and that all issues are being recorded, to perform source data verification, and to monitor drug accountability. The visit intervals will depend on the outcome of the remote monitoring of the CRFs, the study site's recruitment rate, and the compliance of the study site to the protocol and *Good Clinical Practice*. In addition, the CRA will be available for discussions by telephone.

The CRA will verify data entered in the CRF against the source data at regular time intervals. Source data verification requires that the CRA be given direct access to all the source documents. Direct access includes permission to examine, analyse, verify, and reproduce any records and reports that are important to the evaluation of the study.

For all data in the CRFs, it must be possible to verify these against source documents.

## **12 Audits and Inspections**

Authorised personnel from Global Clinical Quality Assurance, H. Lundbeck A/S, and quality assurance personnel from business partners may audit the study at any time to assess

compliance with the protocol and the principles of *Good Clinical Practice*<sup>4</sup> and all other relevant regulations.

The patients must be informed that authorised personnel from Lundbeck may wish to inspect their medical records. The investigator must be aware and the patients must be informed that representatives from regulatory authorities may also wish to inspect source data, such as medical records.

The investigator must notify Lundbeck, without delay, of an announced inspection by a regulatory authority.

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

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

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

## 13 Ethics

### 13.1 Ethical Rationale

Patients will be fully informed about the study including the risks and benefits of his/her participation in the study as well as available alternative therapies.

The patient may withdraw from the study at any time, for any reason, specified or unspecified and without penalty or loss of benefits to which the patient is otherwise entitled. Unscheduled visits can be made and immediate withdrawal is possible. Throughout the study, signs of suicidal risk will be assessed and patients at risk will be withdrawn from the study.

All patients participating in this study will receive an active base treatment for AD. The benefit of this design is that no patient will be exposed to risk of not receiving any treatment.

Patients completing the study may, if eligible, have the option to participate in a 6 month open-label extension study with Lu AE58054 and donepezil.

The risks associated with this study are considered adequately elucidated in the non-clinical and clinical studies, well controlled by cautionary measures in the study design, and well balanced with the potential benefits of the treatment.

Since the study will enrol patients with dementia, special attention must be paid to the procedures for informed consent. Ample time must be given for explanation of the consequences of participation in the study. Detailed local procedures on the informed consent

process for the patient (or, if applicable, the legal representative) and caregiver must fulfil GCP standards, be in accordance with the declaration of Helsinki, and comply with national laws/Ethics Committees requirements.

In accordance with *Good Clinical Practice*,<sup>4</sup> qualified medical personnel at the sponsor or at the CRO will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the Lundbeck Lu AE58054 Safety Committee to ensure that prompt action is taken, if needed, to maximise patient safety.

Furthermore, a Data Monitoring Committee (DMC) has been established for the study. The DMC will provide risk benefit assessments of the study to the sponsor at predefined intervals as further described in the Data Monitoring Committee charter (see section 9.6).

### **13.2 Informed Consent**

No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the patient and/or his or her legal representative and the caregiver.

It is the personal responsibility of the investigator to obtain written informed consent from the patient and/or his or her legal representative and the caregiver.

If parts of the informed consent process (such as giving information) may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

The investigator must identify vulnerable patients, that is, patients whose willingness to participate in a clinical study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

Prior to obtaining written informed consent, the investigator or a designee must explain to potential patients and/or their legal representatives and the caregivers, the aims, methods, and potential hazards of the study and any discomfort it may entail. Patients and/or their legal representatives and the caregiver must be informed that their participation in the study is voluntary and that they are free to withdraw from the study at any time without justifying their decision. Patients and/or their legal representatives and the caregivers must be informed of the possibility of withdrawing consent (section 7.4).

Patients and/or their legal representatives and the caregivers must be given ample time and opportunity to inquire about details of the study prior to deciding whether to participate in the study.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients and/or their legal representatives and the caregivers. Prior to enrolling a patient in the study, an *Informed Consent Form* must be signed and dated by the patient and/or his or her legal representative and the caregiver and the investigator on the same day. The patients and/or their legal representatives and the caregivers will receive a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Consent Form*.

The blood samples may be shared with academic or public institutions; however, Lundbeck will retain full control of the samples and their use in accordance with the information in the *Patient Information Sheet* and a *Material Transfer Agreement*. Furthermore, samples may be pooled across studies to increase the statistical power of the analyses.

### **13.3 Patient Contact Arrangements**

The site personnel will document the patient's living arrangements and working arrangements in the patient's medical records at Visit 1 (Screening Visit). At each subsequent visit, the site personnel will ask appropriate follow-up questions regarding the arrangements. This procedure will be documented in the site initiation visit report and signed by the investigator.

### **13.4 Personal Data Protection**

Data will be processed in accordance with the specifications outlined by the Danish Data Protection Agency to ensure that requirements regarding personal data protection are met and with the legislation in the countries where the patients are recruited. If an external organisation will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organisation to ensure compliance with the above-mentioned legislation.

If applicable, the participation of patients in this study must be reported to the appropriate local data protection agencies, in accordance with European Union Directive 95/46/EC<sup>24</sup> and country-specific guidelines and laws.

### **13.5 Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)**

This study will be conducted only after approval of the protocol has been granted by the appropriate IEC or IRB and a copy of the approval has been received by Lundbeck.

The investigator must not screen any patients before receiving written approval from the IEC or IRB.

The IEC or IRB must be informed of all protocol amendments and must be asked whether a re-evaluation of the ethical aspects of the study is necessary.

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

## 13.6 Regulatory Approval/Notification Requirements

In accordance with local requirements, this study will be submitted to the relevant regulatory authorities for approval or notification. The study will only be undertaken when Lundbeck has received written approval or confirmation of notification from the regulatory authorities.

## 14 Protocol Compliance

Deviations from the protocol must not occur.

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

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

## 15 Study Termination

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

- safety concerns
- proven lack of efficacy of the IMP in other studies

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

If the risk/benefit analysis changes after the termination of the study, the new evaluation must be provided to the IECs and the IRBs if it will have an impact on the planned follow-up of the patients who participated in the study. If so, the actions needed to protect the patients must be described.

## 16 Endpoints

### 16.1 Efficacy Endpoints

#### 16.1.1 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)

### 16.1.2 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-ADL23) total score

### 16.1.3 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 in single NPI items at Week 24
  - Change from baseline to Week 24 in NPI Anxiety item score in patients with an NPI Anxiety score of at least 2 at baseline
- Endpoints that are supportive of the primary objective:
  - Clinical response at Week 24 (ADAS-cog change  $\leq -4$  and ADCS-ADL23 change  $\geq 0$  and ADCS-CGIC  $\leq 4$ )
  - Clinical worsening at Week 24 (ADAS-cog change  $\geq 4$  and ADCS-ADL23 change  $< 0$  and ADCS-CGIC  $> 4$ )
  - Change from baseline to Week 24 in Mini Mental State Examination (MMSE)
  - Change from baseline to Week 24 in EQ-5D utility score
  - Change from baseline to Week 24 in EQ-5D VAS
- Endpoints addressing other objectives:
  - PK assessments (for population PK and PK/PD modelling)

## 16.2 Safety Endpoints

- 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



## 17 Statistical Methodology

### 17.1 Responsibilities

The Department of Biostatistics, H. Lundbeck A/S will perform the statistical analysis of the efficacy and safety data for the *Clinical Study Report*.

Pharmacoeconomic analyses beyond those described in this chapter will be reported separately.

Population pharmacokinetic and pharmacodynamic analyses will be reported separately.

The exploratory biomarker analyses will be reported separately.

### 17.2 Analysis Sets

The following analysis sets will be used for analysis and presentation of the study data:

- *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 double-blind IMP
- *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of ADAS-Cog

Each patient will be classified according to these definitions at a Classification Meeting held after all the data have been entered in the study database and verified and before the randomisation code is broken.

Efficacy analyses will be based on the FAS and summaries of baseline data and safety data will be based on the APTS.

### 17.3 Descriptive Statistics

The data from the clinical assessments, including demographics and other baseline characteristics, will be summarised or listed by treatment group and visit using descriptive techniques. Summary statistics (n, arithmetic mean, standard deviation, median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables (absolute values at each visit and, if relevant, changes from baseline) and counts and, if relevant, percentages will be presented for categorical variables. Where appropriate, the presentation of results will include confidence intervals of estimated treatment differences or plots.

Data will also be presented by MMSE stratum and if relevant by withdrawal status.

## 17.4 Patient Disposition

The number of patients who withdraw from the study will be summarised by treatment group and MMSE stratum, by reason for withdrawal.

Kaplan-Meier time to withdrawal plots will be generated by treatment group and by MMSE stratum.

## 17.5 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarised by treatment group and MMSE stratum.

## 17.6 Recent and Concomitant Medication

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

## 17.7 Exposure

Exposure to IMP will be calculated per patient and summarised by treatment group and MMSE stratum.

## 17.8 Efficacy Analyses

### 17.8.1 Primary Analysis

Changes from baseline in ADAS-Cog of post-baseline assessments at weeks 4, 12, and 24 will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. Analyses will include the fixed, categorical effects of treatment (two doses and placebo), country, visit, treatment-by-visit interaction, MMSE-stratum (<19, ≥19), and MMSE-stratum-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If, unexpectedly, this analysis fails to converge, the following 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 Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary comparisons will be the contrasts between each dose and placebo at the 24 week visit based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between each dose and placebo based on this model will be reported with two-sided symmetric 97,5% confidence intervals and corresponding p-values.

### 17.8.2 Key Secondary Analyses

For the key secondary endpoints, ADCS-CGIC and ADCS-ADL23, the same methodology as that described for the primary analysis 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.

### 17.8.3 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%. The null hypothesis of no difference in mean change from baseline in ADAS-Cog at Week 24 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 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 has to show statistically significant favourable differences compared to placebo at Week 24.

### 17.8.4 Other Secondary Analyses

Changes from baseline in total NPI as well as individual NPI items at week 4, 12, and 24 will be analysed using the same methodology as that described for the primary endpoint. Changes from baseline in NPI Anxiety item score at Week 4, 12, and 24 in the subset of patients with a score of at least 2 at baseline will be analysed using the same methodology as that described for the primary endpoint.

Emergence of individual NPI items at Week 24 for the subset of patients with a baseline score of 0 for the item 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. The analysis will be based on observed cases with no imputation for missing values.

The proportion of patients with clinical response (ADAS-cog change  $\leq -4$  and ADCS-ADL23 change  $\geq 0$  and ADCS-CGIC  $\leq 4$ ) 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 without imputation as well as for the whole FAS, imputing a non-response for all patients discontinued prior to Week 24.

The proportion of patients with clinical worsening (ADAS-cog change  $\geq 4$  and ADCS-ADL23 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 without imputation as well as for the whole FAS, imputing a clinical worsening for all patients discontinued prior to Week 24.

Changes 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. The analysis will be based on observed cases with no imputation for missing values.

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

### **17.8.5 Exploratory Efficacy Analyses**

Sensitivity analyses of the primary and key secondary endpoints:

- MMRM analysis including efficacy data collected at the Withdrawal Follow-up visit for withdrawn patients.
- Pattern-mixture model in which missing values due to dropout in all treatment arms are imputed using multiple imputations from a model based on the placebo group.<sup>1</sup> This model is considered very conservative as it assumes that patients who withdraw differ from those who complete the study and that imputed outcomes (conditional on the past) are the same as those in the placebo group (with the same past).
- MMRM analysis based on patients completing the Week 24 visit.
- For ADCS-CGIC, a non-linear mixed model for ordinal response will be applied to explore sensitivity to the normal distribution assumption for this variable in the primary analysis

Subgroup analyses for the primary and the key-secondary endpoints will be performed by MMSE-stratum. The same methodology as that described for the primary analysis will be used with MMSE-stratum and MMSE-stratum-by-visit interaction terms excluded from the model.

For the primary and key secondary endpoints, 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, applying the same model as that described for the primary endpoint.

### **17.9 Pharmacoeconomic Analyses**

Each item of the RUD-Lite and the dependency level score will be summarised by treatment group. Data will also be presented by MMSE stratum.

Analyses of EQ-5D utility Score and EQ-5D VAS are described in section [17.8.4](#).

### **17.10 Pharmacokinetic and Pharmacodynamic Analyses**

Plasma concentrations of both LuAE58054 and donepezil will be summarised by descriptive statistics by treatment group and visit.

The population pharmacokinetic (popPK) of Lu AE58054 will be determined by means of non-linear mixed effect modelling, demographic information and CYP enzyme phenotype will be tested as covariates in the model.

Individual exposure estimates will be tested for relation with pharmacodynamic parameters (popPK/PD) on an exploratory basis.

The popPK of donepezil will be determined in order to estimate the individual average concentration at steady-state ( $C_{av}$ ).

An analysis plan describing the non-linear mixed effect modelling in more detail will be prepared by H. Lundbeck A/S: Dept of Quantitative Pharmacology in collaboration with Dept of Biostatistics and the results reported separately but referred to in the *Clinical Study Report*, as relevant.

## 17.11 Safety Analyses

### 17.11.1 Analysis of Adverse Events

Adverse events will be classified according to when the adverse event started:

- *pre-treatment adverse event* – an adverse event that starts after the patient signed the *Informed Consent Form* and prior to the first dose of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts after the first dose of IMP and prior to the last protocol-specified contact with that patient. TEAEs may be divided into study periods (these will be defined in the *Statistical Analysis Plan*).

Adverse events, sorted by system organ class (SOC) and preferred term, will be summarised by treatment group.

### 17.11.2 Analysis of Other Safety Variables

The clinical safety laboratory tests, vital signs, weight and ECG parameters will be summarised by treatment group. Potentially clinically significant (PCS) values will be flagged and summarised.

C-SSRS scores will be summarized by treatment group.

### 17.11.3 Analysis of Liver Tests

In addition to the standard summary of clinical safety laboratory tests, the incidences of

- ALT/AST > 1x, 1.5x, 2x, 3x, 5x, 10x, 20x ULN
- TBL > 1x, 1.5x, 2x ULN
- AP > 1.5x, 2x ULN
- ALT/AST > 3xULN and TBL > 2xULN
- ALT/AST > 3xULN and TBL > 2xULN and AP ≤ 1.5xULN

- ALT/AST > 3xULN and (TBL > 2xULN or INR > 1.5xULN) and AP ≤ 1.5xULN

will be produced by treatment group.

### 17.12 Interim Analyses

No interim analyses for efficacy are planned. A DMC will monitor safety data at regular intervals to be specified in the *Data Monitoring Committee Charter*.

### 17.13 Sample Size and Power

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 or ADCS-CGIC, assuming improvements of 2 points on both ADAS-Cog and ADCS-ADL, 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, 0.38 between ADAS-Cog and ADCS-CGIC, and -0.35 between ADCS-ADL and ADCS-CGIC when adjusting for baseline scores. Multiplicity due to multiple doses and endpoints is adjusted for as explained in the Statistical Methodology. The power has been evaluated by simulation from a multivariate normal distribution with the assumed mean and covariance structure described.

### 17.14 Statistical Analysis Plan

A *Statistical Analysis Plan* describing the handling of data issues and the planned statistical analyses in more detail will be prepared by the Department of Biostatistics, H. Lundbeck A/S before the study is unblinded.

## 18 Study Report and Publications

### 18.1 Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by the Department of Medical Writing, H. Lundbeck A/S.

### 18.2 Data Ownership

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

### **18.3 Publications**

The results of this study will be published. Authors of the primary publication based on this study must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).<sup>25</sup>

The primary publication must be published before any secondary publications are submitted for publication.

## **19 Indemnity and Insurance**

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

## **20 Finance**

### **20.1 Site Agreement**

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

### **20.2 Financial Disclosure**

All investigators, including sub-investigators and raters, participating in the study must complete a *Financial Disclosure Form* in order to comply with the United States Food and Drug Administration (FDA) *Financial Disclosure* requirements.

### **20.3 Equipment**

Equipment owned or rented by Lundbeck that has been provided to the site for use during the study must be returned as appropriate, but no later than at the end of the open label extension study (14861B).

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**Appendix I**  
**Clinical Study Protocol**  
**Authentication and Authorisation**

## **Clinical Study Protocol 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

Study No.: 14861A

Edition No.: 3.0

Date of edition: 28 February 2014

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

### **Authentication**

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

International study manager: Cecilia Ericson, PhD

Clinical research scientist: Neli Boneva, MD, PhD

Head, Biostatistics: Anna Karina Trap Huusom, MSc

Divisional Director, GPV: Gitte Frello, MSc, PgD

### **Authorisation**

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

Divisional Director, ICR Neurology: Bjørn Aaris Grønning, MD

**Appendix II**  
**Recent and Concomitant Medication:**  
**Disallowed or Allowed with Restrictions**

## Recent and Concomitant Medication; Disallowed or Allowed with Restrictions

Drug Class	Details
Any investigational drug	Disallowed <60 days before screening or 5 half-lives – whichever is longer, and throughout the whole study.
AChE inhibitors or cholinergic agonists or antagonists	All AChE inhibitors except donepezil are disallowed for 6 months prior to screening and during the study. Treatment with donepezil must have been initiated at least 6 months prior to the Screening Visit. The dose of donepezil must have been stable at 10mg/day for at least 4 months prior to screening. This dose must be maintained throughout the duration of the study.
Anti-cholinergic drugs acting on the muscarinic acetylcholine receptor	Allowed only if prescribed for urinary and bladder difficulties, including frequent urination and inability to control urination. Stable treatment with no modification of dose for at least 3 months prior to the Screening Visit is acceptable. Dose modifications and initiation of treatment are disallowed during the study.
Anaesthetics: General Local	General anaesthetics are disallowed during the study except in case of emergency procedures requiring anaesthesia. Episodic use of local anaesthetics is allowed.
Analgesics	Codeine and tramadol are allowed. Other opioid analgesics are disallowed within 30 days prior to screening and during the study.
Anorexics	Disallowed 6 months prior to screening and during the study
Antiacne agents	Disallowed for 30 days prior to screening and during the study. Agents for topical use are allowed
Antiarrhythmics	Flecainide and propafenone disallowed. For all other antiarrhythmics, stable treatment with no modification of dose for at least 3 months prior to the Screening Visit acceptable. Dose modifications and initiation of treatment allowed during the study. As specified in the donepezil SPC precaution should be taken when administering quinidine.
Antibiotics	Disallowed for chronic use during the study. UTI prophylaxis with antibiotics is allowed.
Anticoagulants	Low dose Low Molecular Weight Heparins for deep vein thrombosis prophylaxis are allowed. The anti-aggregation agents clopidogrel, or aspirin, or dipyridamole are allowed. Other anticoagulants are disallowed during the study.

Drug Class	Details
Anticonvulsants	<p>Disallowed if indication is epilepsy or convulsions. Pregabalin is allowed for treatment of neuropathic pain. Gabapentin is allowed for treatment of neuropathic pain or essential tremor. Treatment must be well tolerated and the dose must have been stable for at least 3 months prior to the Screening Visit and during the study. Initiation of treatment during the study is disallowed.</p> <p>All other anti-epileptic agents are disallowed 6 months prior to screening and during the study, regardless of the indication.</p>
Antidepressants	<p>Stable treatment with no modification of dose with selective serotonin reuptake inhibitors (SSRIs), venlafaxine, moclobemide and mirtazapine for at least 6 months prior to the Screening Visit acceptable. Paroxetine and duloxetine should be used with caution. Dose modifications and initiation of treatment not allowed during the study. Trazodone (maximum <u>evening</u> dose of 50 mg) is acceptable if the treatment is stable with no modification of dose for at least 30 days prior to the Screening Visit. Initiation and dose modification are not allowed during the study. Other antidepressants disallowed from 3 months prior to screening and throughout study. As specified in the donepezil SPC precaution should be taken when administering fluoxetine.</p>
Antidiarrhoeal agents	Allowed except opioid-containing agents.
Antifungal agents: Systemic Topical	<p>Systemic antifungal agents are disallowed for 30 days prior to screening and during the study.</p> <p>Antifungal agents for topical use are allowed</p>
Antihistamines	Only fexofenadine, (dex)loratidine and cetirizine allowed before and throughout the study
Antihypertensives	<p>Centrally active antihypertensives (such as clonidine, alpramethyldopa, guanidine, guanfacine, moxonidine) are disallowed from 30 days prior to screening and throughout study. For all other antihypertensives, dose modifications and initiation of treatment are allowed during the study.</p>
Anti-impotence agents	Disallowed for 30 days prior to screening and during the study.
Antinauseants	Occasional use for up to five consecutive days allowed.
Antineoplastics	Disallowed for 5 years prior to screening and during the study.
Antiobesity agents	Disallowed for 30 days prior to screening and during the study.

<b>Drug Class</b>	<b>Details</b>
Anti-parkinson agents (e.g., levodopa, dopamine agonists, COMT inhibitors, amantadine, monoamine oxidase B inhibitors, anticholinergics etc)	Disallowed for 6 months prior to screening and during the study.
Anti-psoriatic agents	Disallowed for 30 days prior to screening and during the study. Anti-psoriatic agents for topical use are allowed
Antipsychotics depot	Disallowed for 6 months prior to screening and during the study.
Antipsychotics typical	Disallowed for 6 months prior to screening and during the study.
Antipsychotics atypical	Only treatment with risperidone (maximum 2mg/day) or quetiapine (maximum 100mg/day) allowed if absolutely necessary, and if prescribed according to treatment guidelines. Risperidone or quetiapine treatment should not be initiated within 3 days of a study visit with efficacy assessments.
Antiviral agents	Anti-HIV agents are disallowed.
Anxiolytics	The use of benzodiazepines is acceptable if the treatment is stable with no modification of dose for at least 30 days prior to screening. The dose should remain fixed during the study. Where absolutely necessary, benzodiazepine treatment can be initiated as a short-term anxiolytic treatment during the study, as long as the treatment is not initiated within 3 days of a study visit with efficacy assessments. Use of antidepressants is described in the corresponding row.
Benign prostate hyperplasia treatment	Only alpha-1 blockers (Terazosin, Tamsulosin, Doxazosin) and finasteride are permitted. Dose must be stable with no modification of dose for at least 3 months prior to the Screening Visit.
Beta-blockers	Precaution should be taken when administering betablockers.
Cough/cold agents	Only non-opioids and codeine allowed.
H2 blocker/proton pump inhibitors	Stable treatment with no modification of dose for at least 3 months prior to the Screening Visit acceptable. Dose modifications and initiation of treatment allowed during the study.
Hormones, including hormone-replacement therapy	Stable treatment with no modification of dose for at least 3 months prior to the Screening Visit acceptable. Dose modifications and initiation of treatment allowed during the study. Steroids: See separate row.
Hormone suppressants	Stable treatment with no modification of dose for at least 3 months prior to the Screening Visit acceptable. Dose modifications and initiation of treatment allowed during the study.

Drug Class	Details
Hypoglycaemic agents and Insulin	Stable treatment with no modification of dose for at least 3 months prior to the Screening Visit acceptable for oral hypoglycaemic agents and insulin. Dose modifications and initiation of treatment allowed during the study. Rosiglitazone is disallowed.
Hypolipidaemics	Stable treatment with no modification of dose for at least 6 months prior to the Screening Visit acceptable. Dose modifications and initiation of treatment allowed during the study.
Muscle relaxants	Disallowed for 30 days prior to the Screening Visit and for chronic use during the study. Allowed on a p.r.n. basis (not to exceed 5 consecutive days). As specified in the donepezil SPC precaution should be taken when administering neuro-muscular blockers.
NMDA-antagonist (memantine)	Disallowed for 2 months prior to the Screening Visit and during the study.
Psychotropic agents, not otherwise specified (including herbal agents)	Disallowed for 30 days prior to the Screening Visit and during the study. Ginkgo Biloba is allowed if the treatment has been stable with no dose modifications for at least 30 days before the Screening Visit. Initiation and dose modification are not allowed during the study
Sedatives/hypnotics	Zolpidem, zaleplon, and zopiclone: These selected hypnotics are acceptable if the treatment is stable with no modification of dose for at least 30 days prior to the Screening Visit. The dose should remain fixed for the duration of the study. Melatonin is allowed anytime. Where absolutely necessary, these agents may be initiated during the study as long as the treatment is not initiated within 3 days of a study visit with efficacy assessments. Please refer to Anxiolytics for benzodiazepines.
Steroids: Systemic Topical Inhalant	Systemic steroids are disallowed for 3 months prior to the Screening Visit and during the study. Topical and inhalant use allowed before and throughout the study.



## **Appendix III**

### **Non-site Study Personnel and Vendors**

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## Non-site Study Personnel and Vendors

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### Coordinating Investigator

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## **Appendix IV**

### **NINCDS/ADRDA Criteria for Alzheimer's Disease**

## NINCDS/ADRDA Criteria for Alzheimer's Disease

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Associations (NINCDS & ADRDA) in 1984 (*McKhann, G. et al., 1984*)<sup>6</sup> issued a document establishing a standardized clinical criteria for AD:

Criteria for clinical diagnosis of **Probable AD** include:

- Dementia established by clinical exam and documented by the MMSE or Blessed Dementia Scale, confirmed by further neuropsychological tests.
- Deficits in two or more areas of cognition.
- Progressive worsening of memory and other cognitive functions.
- No disturbance of consciousness.
- Onset between the ages of 40 and 90.
- Absence of systemic diseases or other brain diseases that could explain the cognitive changes.

The diagnosis of **Probable AD** is supported by:

- Progressive deterioration of specific cognitive functions such as language, motor skills, and perception (aphasia, apraxia, agnosia, respectively).
- Impaired activities of daily living.
- Positive family history, particularly if documented neuropathologically.
- Lab results: Normal lumbar puncture, EEG, and evidence of cerebral atrophy and CT or MRI.

Other clinical features consistent with diagnosis of Probable AD, after exclusion of other causes of dementia:

- Plateaus in clinical course
- Associated symptoms: depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss.
- Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased motor tone, myoclonus, or gait disorder.
- Seizures in advanced disease.
- CT normal for age.

Features that make the diagnosis of Probable AD **unlikely or uncertain:**

- Sudden apoplectic onset.
- Focal neurological findings such as hemiparesis, sensory loss, visual fields deficits, and incoordination early in the course of illness.
- Seizures or gait disturbances at the onset or very early in the course of the illness.

Clinical diagnosis of **Possible AD**

- May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course.
- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.
- Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

## **Appendix V**

### **NINDS-AIREN Criteria for Vascular Dementia**



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## NINDS-AIREN Criteria for Vascular Dementia

### NINDS-AIREN Criteria for Vascular Dementia

The National Institute of Neurological Disorders and Stroke (NINDS) with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (ARIEN) research criteria for the diagnosis of vascular dementia (VaD) (*Roman, G. C. et al, 1993*)<sup>7</sup>:

I. The criteria for the clinical diagnosis of *probable* vascular dementia include *all* of the following:

- 1) Dementia defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferable established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.  
*Exclusion criteria:* cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
- 2) Cerebrovascular disease, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes*, or *extensive periventricular white matter lesions*, or combinations thereof.
- 3) A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following:
  - a) Onset of dementia within 3 months following a recognized stroke;
  - b) Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II. Clinical features consistent with the diagnosis of *probable* vascular dementia include the following:

- Early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait)
- History of unsteadiness and frequent, unprovoked falls
- Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
- Pseudobulbar palsy
- Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of vascular dementia uncertain or unlikely include

- Early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging
- Absence of focal neurological signs, other than cognitive disturbance
- Absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of *possible* vascular dementia may be made in the presence of dementia (section I-1) with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of definite vascular dementia are (a) clinical criteria for probable vascular dementia; (b) histopathologic evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

The term “AD with CVD” should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term “mixed dementia,” used hitherto, should be avoided.