Clinical Study Protocol

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

Idalopirdine (Lu AE58054)

Phase III

Study No.:	14861B
EudraCT/IND No.:	2013-000001-23/ 118,782
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
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Synopsis – Study 14861B

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Idalopirdine (Lu AE58054)	**EudraCT/IND No.** 2013-000001-23/ 118,782

Title of Study

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

Study Sites and Number of Patients Planned

Open-label treatment period (initial 28-week period):

Approximately 240 sites (hospitals and specialist centres) are planned in 30-35 countries.

Up to 1770 patients with mild-moderate Alzheimer's disease (AD), who have completed Visit 7 (Completion Visit) in one of the lead-in studies.

Open-label treatment period with memantine (substudy):

Approximately 70-90 sites are planned in 13 countries, hospital and specialist centres. Only certain sites within a country will be selected to participate and will depend primarily on the site's potential eligible patient population.

Approximately 100 patients with Alzheimer's disease, who have completed the open-label treatment period (initial 28-week period, i.e., Visit 6).

Objectives

Open-label treatment period (initial 28-week period):

- Primary objective:
  - To evaluate the long term safety and tolerability of idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate AD.
- Secondary objective:
  - To evaluate the disease development during long term treatment with idalopirdine as adjunctive therapy to donepezil.

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

- Primary objective:
  - To evaluate the safety and tolerability of concomitant treatment with idalopirdine, memantine and donepezil in patients with AD.
- Secondary objective:
  - To evaluate the disease development during concomitant treatment with idalopirdine, memantine and donepezil in patients with AD.
- Other objectives
  - To explore population pharmacokinetics

Study Methodology

- This is an interventional, multi-national, multi-site, open-label extension study in patients with mild to moderate AD who completed the 24-week "lead-in" double-blind, placebo controlled clinical studies 14861A and 14862A (from now on these studies will be referred to as “lead-in study” in the document). Investigators will be informed about which treatment their patients received only after the last patient from their respective lead-in study has completed the extension study.
- For sites not participating in the open-label treatment period with memantine (substudy), the study will include one period. For sites participating in the open-label treatment period with memantine (substudy), the study will include two consecutive periods:
  - Open-label treatment period (initial 28-week period): 28-weeks with idalopirdine 60 mg/day as adjunctive treatment to donepezil (10 mg/day). The dose of idalopirdine can be decreased to 30 mg/day if 60 mg/day is not well tolerated in the opinion of the investigator during this 28-week period only. The Baseline Visit of this period (Baseline II) will be the same visit as Visit 7 (Completion Visit) in the lead-in studies.
  - Open-label treatment period with memantine (substudy): 24-weeks with idalopirdine 60 mg/day (or 30 mg/day) [continuation of dose used in open-label treatment period (initial 28-week period)] as adjunctive treatment to donepezil hydrochloride 10 mg/day and memantine (patient’s individualised maintenance dose, including a titration phase of up to 3 weeks). Memantine should be prescribed according to investigator's judgement and the initial dose may be changed at any time throughout the course of the study, if clinically indicated in the opinion of the investigator. The dose and dosing regimen of donepezil and idalopirdine in the 24-week period must remain fixed at that given in the open-label treatment period (initial 28-week period). The Baseline Visit of this period (Baseline III) will be the same visit as Visit 6 in the open-label treatment period (initial 28-week period).
- Patients completing the open-label treatment period (initial 28-week period) and who will not continue into the 24-week open-label treatment period with memantine (substudy) will enter a 4-week safety follow-up period. Thus the total study duration per patient from Baseline II to the end of the follow-up will be approximately 32 weeks.
- Patients completing the two consecutive treatment periods will enter a 4-week safety follow-up period. Thus the total study duration per patient from Baseline II to the end of the follow-up will be approximately 56 weeks.
- The study design is presented in Panel 1 and the scheduled assessments are summarised in Panel 2 and Panel 3.
- An independent Data Monitoring Committee (DMC) will monitor the patients' safety according to the *Data Monitoring Committee Charter*.

Target Patient Population

Open-label treatment period (initial 28-week period):

Major inclusion criteria

- The patient has completed Visit 7 (Completion Visit) in the lead-in study.

Major exclusion criteria

- The patient has a moderate or severe ongoing adverse event from the lead-in study considered a potential safety risk by the investigator.
- The patient has been tested positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus / antibodies (anti-HCV), AND had abnormal ALT, AST or bilirubin in the lead-in study.
- 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 Completion Visit in the lead-in study.
- The patient has one or more clinical laboratory test values outside the reference range, based on the latest available blood and urine sample results, available at the Completion Visit in the lead-in study, that are of potential risk to the patient's safety, or the patient has according to the latest available blood sample:
  - 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.

Open-label treatment period with memantine (substudy):

Major inclusion criteria at Baseline III

- The patient has completed Visit 6 (i.e., the open-label treatment period [initial 28-week period]).
- The patient has a MMSE score at Visit 6 not greater than 19 in accordance with the memantine label/summary of product characteristics (*SmPC*).
- The patient, according to the judgement of the investigator, requires initiation of treatment with memantine as per local label/*SmPC*/treatment guidelines.

Major exclusion criteria at Baseline III

- The patient exhibits an increase in MMSE score by 3 points or more at Visit 6 from Baseline II.
- The patient has a moderate or severe on-going adverse event from the open-label treatment period (initial 28-week period) considered a potential safety risk by the investigator.
- The patient has a previous history of testing positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus / antibodies (anti-HCV) AND had abnormal ALT, AST or bilirubin during the open-label treatment period (initial 28-week period).
- The patient has 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 Visit 6 in the open-label treatment period (initial 28-week period).
- The patient has one or more clinical laboratory test values outside the reference range, based on the latest available blood and urine sample results during the open-label treatment period (initial 28-week period), that are of potential risk to the patient's safety, or the patient has according to the latest available blood sample:
  - 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 >2 times the upper limit of the reference range.

Investigational Medicinal Product, Doses and Mode of Administration

Open-label treatment period (initial 28-week period):

Base treatment:

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

Investigational Medicinal Product (IMP):

Idalopirdine - 60 mg/day (or 30 mg/day); once daily, encapsulated tablets, for oral use.

Open-label treatment period with memantine (substudy):

Base treatments:

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

Memantine immediate-release (IR): 20 mg/day (recommended target dose) or patient's individualised maintenance dose (including titration doses as applicable during an initial titration phase of up to 3 weeks); once daily or twice daily, tablets, for oral use.

Memantine extended-release (XR): 28 mg/day (recommended target dose) or patient's individualised maintenance dose (including titration doses as applicable during an initial titration phase of up to 3 weeks); once daily, capsules, for oral use.

Investigational Medicinal Product (IMP):

Idalopirdine - 60 mg/day (or 30 mg/day); once daily, encapsulated tablets, for oral use.

Memantine will not be supplied by Lundbeck, but should be prescribed according to approved *SmPC*/label by the investigator or another medically-qualified person.

Efficacy Assessments

Open-label treatment period (initial 28-week period):

- Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC)
- Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL_{23})
- Neuropsychiatric Inventory (NPI)
- Mini Mental State Examination (MMSE)

Open- label treatment period with memantine (substudy):

- Mini Mental State Examination (MMSE)

Pharmacoeconomic Assessments

Open-label treatment period (initial 28-week period):

- Resource Utilisation in Dementia – Lite (RUD-Lite)
- EQ-5D-3L
- Dependence scale

Open-label treatment period with memantine (substudy):

- Patient's current living accommodation (question extracted from the Resource Utilisation in Dementia – Lite (RUD-Lite))
- Dependence scale

Pharmacokinetic/Pharmacodynamic/Translational Medicine Assessments

Open-label treatment period with memantine (substudy):

Blood samples for drug plasma concentration analyses of idalopirdine and memantine will be drawn according to the schedule in Panel 3.

Safety Assessments

- Adverse events (AEs)
- Clinical safety laboratory tests
- Vital signs
- Weight/Body Mass Index (BMI)
- Electrocardiograms (ECGs)
- Physical and neurological examinations
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

N/A

Statistical Methodology

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

- all-patients-treated set (APTS) – all patients who took at least one dose of IMP in the open-label treatment period (initial 28-week period).
- all-patients-treated set 2 (APTS2) – all patients who took at least one dose of both IMP and memantine in the open-label treatment period with memantine (substudy).

All analyses in the open-label treatment period (initial 28-week period) will be based on the APTS, and all analyses in the open-label treatment period with memantine (substudy) will be based on APTS2.

Safety and efficacy assessments will be summarised descriptively. On an exploratory basis the development of efficacy assessments in the open-label treatment period (initial 28-week period) will be analysed using Mixed Models for Repeated Measurements (MMRM).

Data will be presented for each treatment period [open-label-treatment period (initial 28-week period) and open-label treatment period with memantine (substudy)] separately for all patients in total as well as by treatment group (placebo or idalopirdine all doses pooled) in the lead-in study, or by lead-in study, and treatment group in the lead-in study.

Sample Size Considerations

Open-label treatment period (initial 28-week period):

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

Open-label treatment period with memantine (substudy):

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

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

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

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.

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.

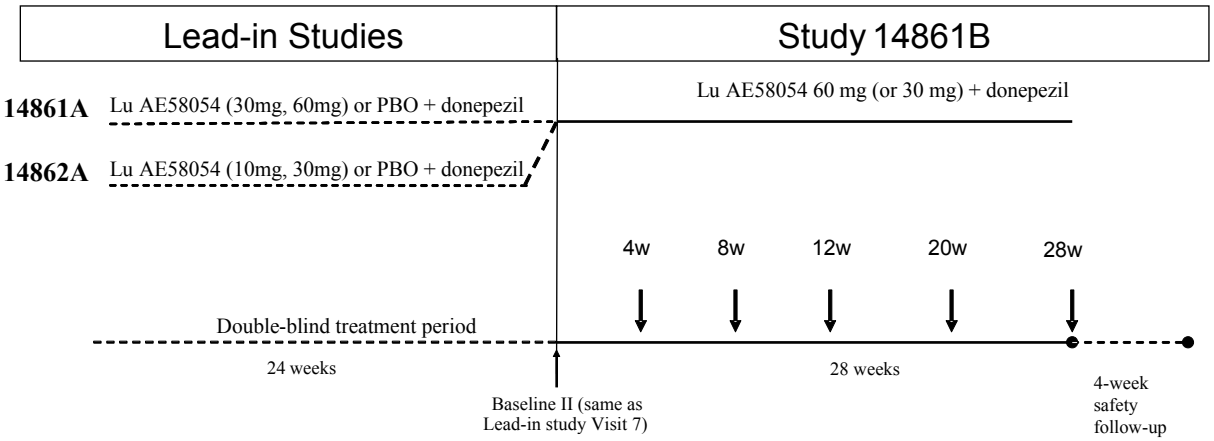
An independent DMC will monitor the patients' safety according to the *DMC Charter*.

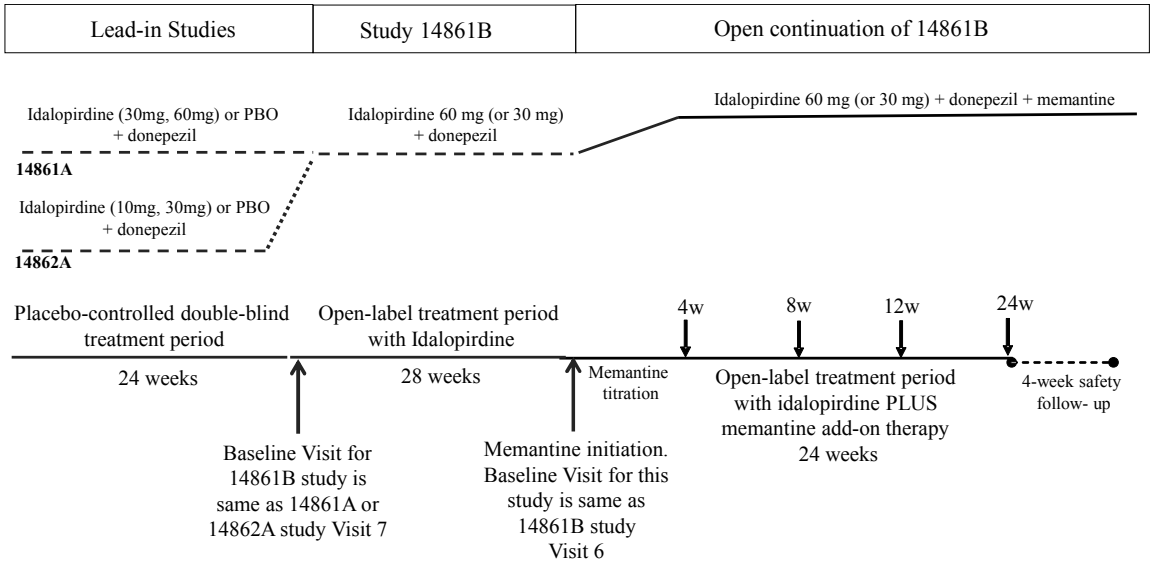
Open- label treatment period with memantine (substudy):

AD is a progressive neurodegenerative disease that is characterised by a steady decline in a patient's cognition and function and an increase in behavioural problems. As patients advance into the moderate stage of AD there may be a need for additional therapy, such as the addition of memantine, to alleviate symptoms that can no longer be managed on the patient's current therapy alone. Thus in a complex disease like AD, there is a strong medical need for alternative treatment options which include combining the different symptomatic treatments with diverse pharmacological modes of action. Concomitant treatment with the three compounds has not been studied in previous or on-going clinical trials. Consequently, it is considered ethical to evaluate the safety and tolerability of adding memantine treatment in patients participating in study 14861B, i.e., in patients who are already on a stable treatment of idalopirdine and donepezil and for whom memantine treatment is clinically indicated.

All patients participating in this study will receive idalopirdine, memantine and donepezil. The study period will allow inclusion of patients for whom the investigator believes that memantine treatment is warranted. Memantine will be prescribed according to the local label/*SmPC*/guidelines meaning that the dose of memantine can be adjusted, if clinically indicated in the opinion of the investigator. In addition, the patients will continue receiving idalopirdine and their donepezil base treatment. Consequently, no patient will be denied access to treatment.

Panel 1 Study Design





Panel 2 Study Procedures and Assessments [open-label treatment period (initial 28-week period)]

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

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

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

Panel 3 Study Procedures and Assessments [open-label treatment with memantine (substudy)]

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

a. The Baseline Visit for this study (Baseline III) is the same visit as Visit 6 (end of Week 28) for patients who complete the open-label treatment period (initial 28-week period).
b. This visit should take place as soon as possible after the patient withdraws from the study.

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

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Appendices

List of Panels

List of Abbreviations and Definitions of Terms

γGT	γ-glutamyl transferase
5-HT	serotonin
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale, cognitive subscale
ADCS-ADL_{23}	Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
ADCS-CGIC	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CIAS	cognitive impairment associated with schizophrenia (CIAS)
C_{max}	maximum observed concentration
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 isoenzyme
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	United States Food and Drug Administration
GABA	gamma-aminobutyric acid
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
NA	not applicable
NPI	Neuropsychiatric Inventory
PBO	placebo
PCS	potentially clinically significant
PR	specific ECG interval describing atrioventricular conduction
QP	qualified person
QRS	specific ECG interval describing ventricular depolarisation
QT_cF	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
SmPC	Summary of Product Characteristics
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TEAE	treatment-emergent adverse event
TID	three times daily
TMF	trial master file
ULN	upper limit of normal

1 Introduction

1.1 Background

1.1.1 Overview

Alzheimer's disease (AD) is an irreversible, chronic and progressive neurodegenerative disease which gradually destroys memory, and the ability to learn, reason, make judgements, 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.

Idalopirdine is a selective serotonin receptor 6 (5-HT_6 receptor) antagonist, which is being jointly developed by H. Lundbeck A/S and Otsuka Pharmaceutical Co, Ltd.. Idalopirdine 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-HT6 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 idalopirdine. Refer to the current version of the *Investigator's Brochure (IB)*[1] for more detailed information.

1.1.2 Non-clinical Data

Idalopirdine is a high affinity antagonist for the 5-HT_6 receptor. Broad profiling of idalopirdine in more than 100 additional assays demonstrated medium affinity to the adrenergic α-1A and α-1B receptors and to the dopamine D3 receptor. Efficacy profiling showed that idalopirdine was an antagonist for the adrenergic α-1A, α-1B and dopamine D3 receptors. For all the remaining targets tested, idalopirdine demonstrated at least 100-fold selectivity.

Idalopirdine has been shown to improve performance in multiple rodent cognition tasks. In doses leading to >65% striatal 5-HT_6 receptor occupancy *in vivo*, idalopirdine reversed

cognitive impairment induced by subchronic phencyclidine in rats. There is no preclinical evidence to demonstrate the cognitive benefits of concomitant treatment of idalopirdine, donepezil and memantine. In microdialysis studies, administration of idalopirdine alone did not affect extracellular levels of GABA, dopamine, 5-HT or acetylcholine (ACh) in the rat prefrontal cortex, whereas idalopirdine (5 mg/kg per os) significantly potentiated donepezil-induced increases in extracellular levels of ACh. This suggests the possibility of synergistic effects when combining idalopirdine with acetylcholine esterase inhibitors.

Safety pharmacology and toxicology studies indicate that at clinically relevant exposure levels, idalopirdine 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 idalopirdine with some contribution from CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Idalopirdine showed inhibitory potential towards CYP2D6. Furthermore, in an *in vitro* study evaluating the induction potential of idalopirdine, idalopirdine 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*.[1]

1.1.3 Clinical Data

Six clinical pharmacology studies and three clinical studies with idalopirdine 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 idalopirdine 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 idalopirdine as augmentation therapy to risperidone in patients with schizophrenia).

The lead-in studies for this protocol (studies 14861A and 14862A) are phase III, randomised, double-blind, parallel-group, placebo-controlled studies designed to evaluate efficacy and safety of idalopirdine over a 24-week period in a total of 1770 patients with mild-moderate AD treated with donepezil.

1.1.3.1 Pharmacokinetics and Pharmacodynamics

In the previous phase II AD study (12936A), the estimated mean idalopirdine 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 metabolised by CYP3A4 and to a minor extent by CYP2D6. In study 12936A, the estimated impact of idalopirdine 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.

The doses in the current phase III clinical program and present study have been selected based on the data from a clinical 5-HT6 receptor occupancy study (in reporting) and simulations in AD patients. 30mg/day and 60 mg/day idalopirdine are predicted to be the clinically effective doses based on the high 5-HT6 receptor occupancy.

1.1.3.2 Efficacy

Idalopirdine 90 mg/day (30 mg TID) was shown to be effective in improving cognitive function in donepezil-treated patients with moderate AD in the study 12936A. This was supported by trends toward improvement in functional and global clinical measures.

1.1.3.3 Safety

Idalopirdine 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, idalopirdine 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 idalopirdine 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 idalopirdine than in patients treated with placebo), were γ-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 idalopirdine group and 7.5% in the placebo group. The differential withdrawal was almost entirely due to elevated liver enzymes test values reported as TEAEs.

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

There were more patients in the idalopirdine 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 idalopirdine 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 these increased liver tests 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, idalopirdine was safe and well tolerated for up to 12 weeks.

Further information on the safety of idalopirdine can be found in the *IB*.[1]

1.2 Rationale for the Study

The lead-in studies aim at establishing the efficacy and safety of idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate AD. The open label extension study will provide supportive long term data on the safety, tolerability and efficacy of idalopirdine. The dose of 60 mg/day is chosen both because of the aim to expose patients to the highest therapeutic dose, which is considered the most relevant for generating safety data, and because of the simplicity of having only one open-label treatment arm. However, a permanent dose decrease to 30 mg/day is allowed, if the dose of 60 mg/day is not well tolerated.

AD is a progressive neurodegenerative disease that is characterised by a steady decline in a patient's cognition and function and an increase in behavioural problems. Thus in a complex disease like AD, there is a strong medical need for alternative treatment options which include combining the different symptomatic treatments with diverse pharmacological modes of action. The open-label treatment period with memantine (substudy) will evaluate the safety and tolerability of adding memantine therapy in patients who are already on a stable treatment of idalopirdine and donepezil and for whom memantine treatment is clinically indicated. Concomitant treatment with the three compounds has not been studied in previous or on-going clinical trials. Furthermore, adjunctive treatment with memantine is likely to be a common treatment option for patients with AD soon after idalopirdine becomes available. Thus the open-label treatment period with memantine (substudy), in the current study, is designed to inform potential future clinicians and patients of the safety and tolerability profile to expect when the three compounds are used concomitantly.

2 Objectives

2.1 Primary Objective

Open-label treatment period (initial 28-week period):

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

Open-label treatment period with memantine (substudy):

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

2.2 Secondary Objective

Open-label treatment period (initial 28-week period):

To evaluate the long term disease development during treatment with idalopirdine as adjunctive therapy to donepezil.

Open-label treatment period with memantine (substudy):

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

2.3 Other Objectives

Open-label treatment period with memantine (substudy):

To explore population pharmacokinetics.

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[2]

This is an interventional, multi-national, multi-site, open-label extension study in patients with mild to moderate AD, who completed Visit 7 (Completion Visit) in the lead-in study. The Baseline II Visit is the same visit as Visit 7 (Completion Visit) in the lead-in study. Investigator will be informed about which treatment their patients received only after the last patient from their respective lead-in study has completed the extension study.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[3] and applicable regulatory requirements.

Approximately 240 sites (hospitals or specialist centres) are planned in 30-35 countries. Up to 1770 patients with mild-moderate AD, who have completed Visit 7 (Completion Visit) in the lead-in study may be eligible for the 14861B study. For the open-label treatment period with memantine (substudy) approximately 100 patients, who have completed the open-label treatment period (initial 28-week period, i.e., Visit 6); will be enrolled if they consent to continue and if they fulfil all inclusion and none of the exclusion criteria at the Baseline III Visit. Thus approximately 70-90 sites in 13 countries are planned to participate (hospitals or specialist centres) in the open-label treatment period with memantine (substudy). Only certain sites within a country will be selected to participate and will depend primarily on the site's potential eligible patient population.

For sites not participating in the open-label treatment period with memantine (substudy), the study will include one period. For sites participating in the open-label treatment period with memantine (substudy), the study will include two consecutive periods:

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

Patients completing the open-label treatment period (initial 28-week treatment period) and who will not continue into the 24-week open-label treatment period with memantine (substudy) will enter a 4-week safety follow-up period. Thus the total study duration per patient from Baseline II to the end of the follow-up will be approximately 32 weeks.

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

A Safety Follow-up Visit will be performed 4 weeks (+ up to 7 days) after the Completion/Withdrawal Visit, whether completion or withdrawal.

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 Safety Follow-up Visit 4 weeks (+ up to 7 days) after the Withdrawal Visit in order to follow-up on safety 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.

An overview of the study is presented in Panel 1 and the scheduled assessments are summarised in Panel 2 [open-label treatment period (initial 28-week period)] and Panel 3 [open-label treatment period with memantine (substudy)].

A Data Monitoring Committee (DMC) has been established for this study. The DMC will provide risk benefit assessments of the study to the sponsor at predefined intervals as further described in the *DMC Charter* (see section 10.6.1).

3.2 Rationale for the Study Design

This study is designed as a classic open-label extension study with add-on design to evaluate the long term safety and tolerability of idalopirdine as adjunctive therapy to donepezil in patients with mild-moderate AD.

The study population will comprise AD patients who have completed Visit 7 (Completion Visit) in the lead-in study.

All patients will receive a dose of (60 mg/day) of idalopirdine, with a possibility to permanently decrease the dose to 30 mg/day if 60 mg/day is not well tolerated in the opinion of the investigator.

The doses of idalopirdine allowed in the study are considered to be safe and well tolerated based on prior clinical data.

It is expected that majority of the patients will be exposed to 60 mg/day for the first time; therefore the safety assessments in this study will be identical to the safety assessments in the lead-in studies.

The open-label treatment period with memantine (substudy) will be offered to patients who have already been exposed to idalopirdine for 6-12 months and for whom memantine treatment is clinically indicated, and will allow them to continue with their idalopirdine treatment (60 mg/day or 30 mg/day) for a further 6 month period.

Thus the design offers a highly relevant platform, as patients will have received at least 6 months of idalopirdine treatment prior to the addition of memantine and provides the ability to compare safety and tolerability, within the same patient, before and after the addition of memantine.

4 Ethics

4.1 Ethical Rationale

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

The patient may withdraw from the study at any time, for any reason, specified or unspecified and without penalty or loss of benefits to which the patient is otherwise entitled. 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 idalopirdine and donepezil. Furthermore, during the open-label treatment period (initial 28-week period), the dose of idalopirdine can be decreased to 30 mg/day if 60 mg/day is not well tolerated in the opinion of the investigator.

The 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*,[2] and comply with national laws/Ethics Committees requirements.

In accordance with *Good Clinical Practice*,[3] qualified medical personnel at the sponsor or at the Clinical Research Organisation (CRO) will be readily available to advice on study-related medical questions. Medical monitoring will be performed throughout the study. Safety data will be reviewed regularly by the Lundbeck Idalopirdine Safety Committee to ensure that prompt action is taken, if needed, to maximise patient safety.

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 10.6.1).

Open-label treatment period with memantine (substudy):

All patients participating in the open-label treatment period with memantine (substudy) will receive idalopirdine, memantine and donepezil. The study period will allow inclusion of patients for whom the investigator believes that memantine treatment is warranted. As patients advance into the moderate stage of AD there may be a need for additional therapy, such as the addition of memantine, to alleviate symptoms that can no longer be managed on the patient's current therapy alone. By participating in the study period the patient would provide important safety and tolerability information when idalopirdine, memantine and

donepezil are used concomitantly. Memantine will be prescribed according to the local label/*SmPC*/guidelines meaning that the dose of memantine can be adjusted, if clinically indicated in the opinion of the investigator. In addition, the patients will continue receiving idalopirdine and their donepezil base treatment for a further 6-month period. Consequently, no patient will be denied access to treatment. In summary, it is considered ethical to evaluate the safety and tolerability of adding memantine treatment in patients participating in study 14861B, i.e., in patients who are already on a stable treatment of idalopirdine and donepezil and for whom memantine treatment is clinically indicated. It is important to consider that all patients in study 14861B would be discharged after trial participation and be able to continue on whichever therapy, including memantine, if clinically indicated by the investigator.

4.2 Informed Consent

No study-related 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 this study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

Prior to obtaining written informed consent, the investigator or a designee must explain to the patients and/or their legal representatives and the caregivers, the aims, methods, and potential hazards of the study and any discomfort it may entail. The patients and/or their legal representatives and the caregivers 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. The patients and/or their legal representatives and the caregivers must be informed of the possibility of withdrawing consent (section 8.3).

The 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 including 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

signed and dated by the investigator on the same day. The patients and/or their legal representatives and the caregivers must receive a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Consent Form*.

Open-label treatment period with memantine (substudy):

The open-label treatment period with memantine (substudy) is optional and will only be required for patients who meet the eligibility criteria for this part of the study and consent to continue.

The principles of consent outlined above also apply to the open-label treatment period with memantine (substudy). The investigator must obtain a separate written *Informed consent* from the patient and/or his or her legal representative and their caregivers before any procedures related to the open-label treatment period with memantine (substudy) are performed.

It is suggested that the *Informed Consent Form* is provided at Visit 5 of the open-label treatment period (initial 28-week period) for patients who may potentially be eligible and who wish to participate in the open-label treatment period with memantine (substudy).

The patients and/or their legal representatives and the caregivers must receive a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Consent Form* for this open-label treatment period with memantine (substudy).

4.3 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. At each subsequent visit, the site personnel will ask appropriate follow-up questions regarding the arrangements and who the patient has been in contact with on a regular basis; the contact's name does not need to be recorded. Details documenting the contact will be recorded in the patient's medical records. This procedure will be documented in the *Site Initiation Visit Report* and signed by the investigator.

4.4 Personal Data Protection

In accordance with *European Union Directive 95/46/EC*,[4] the 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. 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 will be reported to the appropriate local data protection agencies, in accordance with *European Union Directive 95/46/EC* and country-specific guidelines and laws.

4.5 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 written approval has been received by Lundbeck.

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

The IEC or IRB must be informed when specific types of protocol amendments have been made 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.

4.6 Regulatory Approval/Notification Requirements

In accordance with local requirements, this study will be submitted to the 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.

5 Study Population

5.1 Numbers of Patients and Sites

This study will include eligible patients who have completed Visit 7 (Completion Visit) in the lead-in study (maximum 1770 patients). Approximately 240 sites (hospitals and specialist centres) are planned in 30-35 countries.

Approximately 100 patients with Alzheimer's disease, who have completed the open-label treatment period (initial 28-week period), will be enrolled into the open-label treatment period with memantine (substudy). Approximately 70-90 sites in 13 countries (Bulgaria, Canada, Czech Republic, Estonia, Germany, France, Italy, Lithuania, Poland, South Korea, Spain, United Kingdom and United States) are planned to participate (hospital and specialist centres). Only certain sites within a country will be selected to participate and will depend primarily on the site's potential eligible patient population.

5.2 Patient Recruitment

Open-label treatment period with memantine (substudy):

As 100 patients are expected to be enrolled in the open-label treatment period with memantine (substudy), the recruitment for this treatment period will end prior to the global recruitment period for the open-label treatment period of study 14861B.

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

Distribution of enrolled patients will be monitored closely to ensure there is a balanced representation of patients across regions.

5.3 Selection Criteria

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

Patients who meet each of the inclusion criteria at the Baseline II Visit and none of the exclusion criteria at the Baseline II Visit are eligible to participate in this study.

Open-label treatment period (initial 28-week period):

Inclusion Criteria

1. The patient has completed Visit 7 (Completion Visit) in the lead-in study.
2. The patient's sight and hearing (hearing aid permissible) are, in the investigator's judgement, sufficient for compliance with the study procedures.
3. 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.*
4. 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*.
5. The patient is willing and able to attend study appointments within the specified time windows.
6. The patient has a knowledgeable and reliable caregiver who will accompany the patient to all clinic visits during the study.
7. The patient, if a man, must:
   - use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline II Visit to ≥1 month after the last dose of IMP, OR
   - have been surgically sterilised prior to the Completion Visit in the lead-in study.

Exclusion Criteria

1. The patient has experienced seizures before Completion Visit in the lead-in study.
2. 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* (*SmPC*) special precaution is needed for patients with asthma, obstructive pulmonary disease, bradycardia, or difficulty in passing urine.

3. 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.
4. The patient's donepezil treatment is likely to be interrupted or discontinued during the study.
5. The patient is receiving therapy with another AChEI or memantine.
6. The patient has clinically significant abnormal vital signs at the Completion Visit in the lead-in study considered a potential safety risk by the Investigator.
7. The patient has a moderate or severe on-going adverse event from the lead-in study considered a potential safety risk by the investigator.
8. The patient has been tested positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus/antibodies (anti-HCV), AND had abnormal ALT, AST or bilirubin in the lead-in study.
9. 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 Completion Visit in the lead-in study.
10. The patient has one or more clinical laboratory test values outside the reference range, based on the latest blood and urine sample results, available at the Completion Visit in the lead-in study, that are of potential risk to the patient's safety, or the patient has according to the latest available blood sample:
    - 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.
11. The patient has, based on the latest ECG results, available at the Completion Visit in the lead-in study:
    - 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, based on the latest ECG results, available at the Completion Visit in the lead-in study, must be discussed with the sponsor medical expert before being enrolled. 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.
12. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.
13. The patient has attempted suicide within the last 6 months or is at significant risk of suicide (either in the opinion of the Investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behaviour on the C-SSRS within the last 12 months).

Open-label treatment period with memantine (substudy):

Patients who meet each of the inclusion criteria at the Baseline III Visit and none of the exclusion criteria at the Baseline III Visit are eligible to participate in the open-label treatment period with memantine (substudy).

Inclusion Criteria

1. The patient has completed Visit 6 [(i.e., the open-label treatment period (initial 28-week period)].
2. The patient's sight and hearing (hearing aid permissible) are, in the investigator's judgement, sufficient for compliance with the study procedures.
3. 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.*
4. 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*.
5. The patient is willing and able to attend study appointments within the specified time windows.
6. The patient has a MMSE score at the Baseline III Visit of this study not greater than 19 in accordance with the memantine label/*summary of product characteristics (SmPC*).
7. The patient, according to the judgement of the investigator, requires initiation of treatment with memantine as per local label/*SmPC*/treatment guidelines.
8. The patient has a knowledgeable and reliable caregiver who will accompany the patient to all clinic visits during the study.
9. The patient, if a man, must:
   - use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline III Visit of this study to ≥ 1 month after the last dose of IMP, OR
   - have been surgically sterilised prior to Visit 6.

Exclusion Criteria

1. The patient exhibits an increase in the MMSE score by 3 points or more at Visit 6 from Baseline II Visit.
2. The patient has experienced seizures before Visit 6.
3. 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 will follow a routine check-up with their doctor and are considered stable. As specified in the donepezil *SmPC* special precaution is needed for patients with asthma, obstructive pulmonary disease, bradycardia, or difficulty in passing urine.
4. The patient has known fructose intolerance.
5. The patient has had safety and tolerability issues with the prior use of memantine.
6. 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.
7. The patient's donepezil or memantine treatment is likely to be interrupted or discontinued during the study.
8. The patient has clinically significant abnormal vital signs at Visit 6 considered a potential safety risk by the Investigator.
9. The patient has a moderate or severe on-going adverse event from the open-label treatment period (initial 28-week period) considered a potential safety risk by the investigator.
10. The patient has a previous history of testing positive for hepatitis B surface antigen (HBsAg), or hepatitis C virus / antibodies (anti-HCV) AND had abnormal ALT, AST or bilirubin during the open-label treatment period (initial 28-week period).
11. The patient has 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 Visit 6 in the open-label treatment period (initial 28-week period).
12. The patient has one or more clinical laboratory test values outside the reference range, based on the latest available blood and urine sample results available at Visit 6, that are of potential risk to the patient's safety, or the patient has according to the latest available blood sample:
    - 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 >2 times the upper limit of the reference range
13. The patient has, based on the latest ECG available at Visit 6:
    - 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/RR0.33)

Patients with a heart rate between 45 and 49 beats per minute or a PR interval between 250 and 280 ms, based on the latest ECG results, available at Visit 6, must be discussed with the sponsor medical expert before being enrolled. 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.

14. The patient is, in the investigator's opinion, unlikely to comply with the protocol, e.g., unable to complete all relevant assessments including the C-SSRS at Visit 6 or is unsuitable for any other reason (e.g., worsening of the patient's dementia to the degree that a change in the patient's residential status is warranted over the next 6 months).
15. The patient is likely to be placed in a nursing home during the study.
16. 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 last 12 months).

5.4 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 8.3 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.
- 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, nauseas, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).*
- the patient has a QTcF interval >500 ms that is confirmed with an ECG taken 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 withdrawn 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"*[5]

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products

6.1 Treatment Regimen

Open-label treatment period (initial 28-week period):

All patients will be treated with idalopirdine 60 mg/day (IMP) and donepezil hydrochloride (10 mg/day).

The daily dose of idalopirdine 60 mg/day can be decreased to 30 mg/day if it is not well tolerated by the patient in the opinion of the investigator (see section 8.6).

The IMP will be dispensed as adjunctive treatment to the base treatment with donepezil hydrochloride.

Visit 1: The patient will be dispensed one wallet card of idalopirdine 60 mg encapsulated tablets and one wallet card of donepezil hydrochloride 10 mg tablets.

Visit 2-3: The patient will be dispensed one wallet card of idalopirdine 60 mg or 30 mg encapsulated tablets and one wallet card of donepezil hydrochloride 10 mg tablets.

Visit 4-5: The patient will be dispensed two wallet cards of idalopirdine 60 mg or 30 mg encapsulated tablets, and two wallet cards of donepezil hydrochloride 10 mg tablets.

The patients will be instructed to take 1 capsule of IMP once daily and 1 tablet of donepezil hydrochloride 10 mg once daily, for oral use. The first dose of the IMP and donepezil hydrochloride 10 mg is to be taken the day after dispensing to the patient. The dose of donepezil hydrochloride must be maintained throughout the duration of the study.

Open-label treatment period with memantine (substudy):

All patients will be treated with the same dose of IMP idalopirdine used in the open-label treatment period (initial 28-week period), donepezil hydrochloride 10 mg/day and memantine (patient's individualised dose; including titration doses).

Memantine (patient's individualised maintenance dose) should be prescribed according to the investigator's judgement and the initial dose may be changed at any time if clinically indicated in the opinion of the investigator. The dose of donepezil hydrochloride must be maintained throughout the duration of the study. The dose of idalopirdine must remain fixed at that the dose given at the end of the open-label treatment period (initial 28-week period). The investigator should ensure that the memantine prescribed to the patient is an approved brand for their country and that an adequate supply of memantine is prescribed for the time between any two visits.

The IMP and memantine will be dispensed as adjunctive treatment to donepezil hydrochloride.

Visit 6, 8-10: Memantine will be prescribed according to the investigator's judgement (patient's individualised dose after titration period) and investigator should ensure that an adequate supply of memantine is prescribed for the patient between any two visits.

Visit 6, 8 and 9: The patient will be dispensed one wallet card of idalopirdine 60 mg or 30 mg encapsulated tablets, one wallet card of donepezil hydrochloride 10 mg tablets.

Visit 10: The patient will be dispensed three wallet cards of idalopirdine 60 mg or 30 mg encapsulated tablets, three wallet cards of donepezil hydrochloride 10 mg tablets.

The patient will be instructed to take 1 capsule of IMP once daily, 1 tablet of donepezil hydrochloride 10 mg once daily, for oral use, and memantine as prescribed by the investigator. The first dose of IMP, and donepezil hydrochloride 10 mg, and memantine is to be taken the day after Visit 6. For the day of Visit 6, patient will take IMP and donepezil from wallet cards that they return and will start new wallet cards the day after Visit 6.

The patient should continue to take memantine from the same supply brought to the visit (for accountability) until the package is empty. The investigator must ensure a new prescription for memantine is provided if there is not enough medication for the treatment days until the next visit including the potential visit window.

Panel 4 Dose Schedules

IMP Dispensing Week	Day/Visit	Treatment Group: Idalopirdine 30 mg or 60 mg/day	Base treatment: Donepezil hydrochloride 10 mg/day	Base treatment: Memantine [a, b] (patient's individualised dose
Week 1	Day 0/ Visit 1	60 mg	10 mg	NA
Week 4	Day 28/Visit 2	30 mg or 60 mg	10 mg	NA
Week 8	Day 56/Visit 3	30 mg or 60 mg	10 mg	NA
Week 12	Day 84/Visit 4	30 mg or 60 mg	10 mg	NA
Week 20	Day 140/Visit 5	30 mg or 60 mg	10 mg	NA
Week 28	Day 196/Visit 6[a]	30 mg or 60 mg	10 mg	titration dose
Week 32	Day 224/Visit 8[a]	30 mg or 60 mg	10 mg	maintenance dose
Week 36	Day 252/Visit 9[a]	30 mg or 60 mg	10 mg	maintenance dose
Week 40	Day 280/Visit 10[a]	30 mg or 60 mg	10 mg	maintenance dose

a only for patients participating in the open-label treatment period with memantine (substudy)

b memantine will be prescribed by the investigator or another medically-qualified person

6.2 IMPs, Formulations, and Strengths

Open-label treatment period (initial 28-week period):

The IMPs in this period are:

- Idalopirdine - 30 mg/day, once daily, encapsulated tablets, for oral use
- Idalopirdine - 60 mg/day, once daily, encapsulated tablets, for oral use

Base treatment provided by H. Lundbeck A/S in this study is:

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

Open-label treatment period with memantine (substudy):

The IMPs in this period are:

- Idalopirdine - 30 mg/day, once daily, encapsulated tablets, for oral use
- Idalopirdine - 60 mg/day, once daily, encapsulated tablets, for oral use

Base treatment provided by H. Lundbeck A/S in this study is:

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

Base treatment prescribed according to investigator judgement is:

- Memantine immediate-release (IR): 20 mg/day (recommended target dose) or patient's individualised maintenance dose (including titration doses as applicable during an initial titration phase of up to 3 weeks); once daily or twice daily, tablets, for oral use.
- Memantine extended-release (XR): 28 mg/day (recommended target dose) or patient's individualised maintenance dose (including titration doses as applicable during an initial titration phase of up to 3 weeks); once daily, capsules, for oral use.

Memantine will not be supplied by Lundbeck, but should be prescribed according to approved *SmPC*/label by the investigator or another medically-qualified person.

6.3 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 tablets 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 idalopirdine 30 mg and idalopirdine 60 mg will be provided in 4-week wallet cards containing 28+7 capsules to account for the treatment period as per Panel 2, Panel 3 and Panel 4.

The donepezil hydrochloride will be provided in 4-week wallet cards containing 28+7 tablets to account for the treatment period as per Panel 2, Panel 3 and Panel 4.

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, 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.

Patients continuing into the open-label treatment period with memantine (substudy) will receive memantine (titration dose or patient's individualised dose) as prescribed according to the Investigator's judgement.

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

6.4 Dispensing of IMP

Open-label treatment period (initial 28-week period):

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

Capsule and tablet counts will be done at each visit. The patients will be asked to return all wallet cards (used and unused) at each visit.

Open-label treatment period with memantine (substudy):

The number of days between two visits must not exceed the number of days for which the patient has been dispensed IMP, donepezil hydrochloride and prescribed memantine.

Capsule and tablet counts will be done at each visit. The patients will be asked to return all wallet cards (used and unused) for IMP and donepezil hydrochloride at each visit. In addition, patients will be asked to bring used and unused memantine in original packaging to the visit for accountability purposes.

6.5 Method of Assigning Patients to Treatment

The patient's screening number from the lead-in study will automatically be transferred into the extension study.

An interactive voice response system (IVRS) will be used in this study. The IVRS will dispense IMP idalopirdine 60 mg (or idalopirdine 30 mg in case of a tolerability issue) to the patients and donepezil hydrochloride 10 mg to the patients on base treatment with donepezil only.

6.6 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

Open-label treatment period with memantine (substudy):

Memantine must be tracked using:

- a patient-specific log to track what is prescribed to, returned by and re-dispensed or re-prescribed to the patient

The investigator and the pharmacist (if applicable) must agree to only dispense IMP and donepezil hydrochloride to 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 record must be available for inspection at any time.

For tracking of accountability, the used and unused wallet cards (IMP and donepezil hydrochloride) and prescribed memantine records should be available for verification of accountability data at any time.

6.7 Post-study Access to IMP

Open-label treatment period (initial 28-week period):

The patients will not be provided with IMP or donepezil hydrochloride after study completion. The patient must be treated in accordance with normal clinical practice and may continue on donepezil hydrochloride as per prescription, if judged relevant by the investigator.

Open-label treatment period with memantine (substudy):

The patients will not be provided with IMP or donepezil hydrochloride after study completion. The patient must be treated in accordance with normal clinical practice and may continue on donepezil hydrochloride and/or memantine as per prescription, if judged relevant by the investigator.

7 Concomitant Medication

For patients in the open-label treatment period (initial 28-week period): Concomitant medication is any medication other than the IMP and donepezil that is taken during the study.

For patients in the open-label treatment period with memantine (substudy): Concomitant medication is any medication other than the IMP, and donepezil and memantine that is taken during the study.

The concomitant medications that are disallowed during the study are summarised in Appendix II.

Data on concomitant medications that are on-going at V7 (Completion Visit) of the lead-in study will be transferred to the 14861B study. Any changes, including reason for the change, 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.

8 Study Visit Plan

8.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 2 and Panel 3. Further details are in chapter 9.

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

8.2 Baseline II Visit /Visit 1 (Visit 7 of the lead-in study)

Baseline II Visit is the same visit as Visit 7 (Completion Visit) of the lead-in study and most of the data from assessments performed during Visit 7 (Completion Visit) will be transferred to study 14861B.

Laboratory and ECG results that are available at Visit 7 (Completion Visit) of the lead-in study will be used for eligibility assessment in study 14861B.

A written *informed consent* must be obtained before any assessments presented in Panel 2 for the Baseline II Visit is performed (with exception of the assessments performed in the lead-in study).

Assessments and procedures to be performed after the *informed consent* has been signed include evaluation of inclusion and exclusion criteria, dispense of *Patient Identification Card* and IMP dispense.

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.

8.3 Baseline III Visit /Visit 6 [open-label treatment period with memantine (substudy)]

Baseline III Visit of the open-label treatment period with memantine (substudy) is the same visit as Visit 6 of the open-label treatment period (initial 28-week period). Assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

The most recent laboratory and ECG results that are available at Visit 6 will be used for eligibility assessment in the open-label treatment period with memantine (substudy).

A *written informed consent* must be obtained before any assessments presented in Panel 3 are performed (with exception of the assessments performed as a part of Visit 6).

Assessments and procedures to be performed after the *informed consent* has been signed include evaluation of inclusion and exclusion criteria, pharmacokinetic assessments and IMP and donepezil dispensing and memantine prescriptions.

8.4 Withdrawal Visit

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

No new information will be collected from patients who withdraw, except information collected in relation to the scheduled Withdrawal Visit or needed for the follow-up of adverse events (section 10.5).

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

For a patient and/or his or her legal representative who withdraw(s) 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 (if applicable) 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 (if applicable) explicitly request(s) that his or her data collected from the time of withdrawal of consent onwards not be used, this will be respected.

8.5 Safety Follow-up Visit (Visit 7 and Visit 12)

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 must be conducted as a visit to the site.

Open-label treatment period (initial 28-week period):

For patients not continuing into the open-label treatment period with memantine (substudy), the safety follow-up (Visit 7) must be conducted 4 weeks (+ up to 7 days) after Visit 6 (Completion/Withdrawal Visit).

Open-label treatment period with memantine (substudy):

The safety follow-up (Visit 12) must be conducted 4 weeks (+ up to 7 days) after Visit 11 (Completion/Withdrawal Visit).

For adverse events that were on-going 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 on-going at the safety follow-up, the stop date must be recorded as "on-going". 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 I values or a diagnosis has been established (see sections 8.7 and 9.4.2). The results must be recorded in the eCRF until the end of the study (see section 8.7).

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.

8.6 Unscheduled Visit (Dispensing Unscheduled Study Visit)

Applicable only to the open-label treatment period (initial 28-week period):

In case of a tolerability issue as per investigator's assessment, the dose of idalopirdine can be decreased from 60 mg/day to 30 mg/day. This is allowed only once during the patient's participation in the study and can only take place during one of already scheduled visits or a specific unscheduled study visit, called "Dispensing unscheduled study visit", to which both the patient and the caregiver are present.

At the "Dispensing unscheduled study visit" the investigator will collect information about the tolerability issue that is to be recorded as an adverse event and potential change in the concomitant medication. The patients will be asked to return the wallet card of idalopirdine 60 mg encapsulated tablets (used and unused) and will be dispensed a new wallet card of idalopirdine 30 mg encapsulated tablets.

8.7 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 on-going in the study.

For any increased (abnormal) laboratory value still present at the time of the last study patient's visit [i.e., Visit 7 for patients who do not continue into the open-label treatment period with memantine (substudy) or Visit 12 for patients who participate in the open-label treatment period with memantine (substudy)], 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.

9 Assessments

9.1 Baseline Procedures and Assessments

Demographics and Other Baseline Characteristics

As indicated in Panel 2, demographics and other baseline characteristics performed during the Screening/Baseline I Visit in the lead-in study will be transferred to the 14861B study, provided the patient is found eligible and has signed the *Informed Consent Form* for the 14861B study.

9.1.1 Use of Efficacy Assessments

- The following assessments will be used: MMSE – assessing the cognitive aspects of mental function
- ADAS-Cog – assessing cognitive impairment
- ADCS-CGIC – blinded assessment of clinical global impression of change
- ADCS-ADL_{23} − 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*.

The ADAS-Cog should preferably be the first efficacy assessment performed at each visit.

The same order of assessments should be used per patient at each visit.

Assessments done at Visit 7 (Completion Visit) of the lead-in study will be transferred and will not be completed at the Baseline II Visit.

For patients continuing into the open-label treatment period with memantine (substudy), MMSE done at Visit 6 in the open-label treatment period (initial 28-week period) is the same as the Baseline III Visit.

9.1.1.1 Mini Mental State Examination (MMSE)

The MMSE[6] 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.

9.1.1.2 Alzheimer's Disease Assessment Scale – cognitive sub-scale (ADAS-Cog)

The ADAS-Cog[7] is a test designed to assess cognitive symptoms associated with AD and is devised to be sensitive to change. The ADAS-Cog consists of 11 items to assess the patients 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.

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

The ADCS-CGIC[8] is a semi-structured interview designed to assess clinically relevant changes in patients with AD. The ADCS-CGIC interview is guided by probes covering cognition, behaviour, and social and daily functioning. The severity of the symptoms is based on answers from both the patient and the caregiver. A global clinical judgement of severity at baseline in the lead-in study 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, which is in this study the baseline assessment performed in the lead-in study.

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. 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 investigator trial master file (TMF) throughout the study.

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

The ADCS-ADL_{23}[9] is a standardised, clinician-rated inventory designed to assess activities of daily living (ADL) in patients with AD over a defined period.

The ADCS-ADL_{23} 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_{23} (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_{23} 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_{23}.

9.1.1.5 Neuropsychiatric Inventory (NPI)

The NPI[10,11,12] 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 $score_{12items}$ of the frequency and severity ratings range from 0 to 144 and the total $score_{12items}$ 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.

9.1.2 Rater Qualification

Only raters who have been trained and certified are allowed to rate patients in study 14861B. The documentation of training issued during the lead-in study covers the extension study 14861B and no additional documentation will be re-issued for existing raters.

Rater training and certification will be conducted by ePharmaSolutions.

9.1.3 For new raters joining the study

The ADAS-Cog and MMSE should only be administered by a rater having adequate experience with patients with AD and administration of cognitive tests. The rater should be a neurologist, geriatrician, psychiatrist or (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_{23} and NPI should only be administered by a rater having adequate experience with patients with AD and administration of (semi-)structured interviews. The rater should be a neurologist, geriatrician, psychiatrist or (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 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.

Exceptional situations must be discussed and approved by the Scales Manager.

9.2 Pharmacoeconomic Assessments

The following pharmacoeconomic assessments will be used:

Open-label treatment period (initial 28-week period):
- EQ-5D-3L (by proxy) – assessing quality of life
- RUD Lite – assessing healthcare resource utilisation
- Dependence scale – assessing dependence

Assessments done at Visit 7 (Completion Visit) of the lead-in study will be transferred and will not be completed at the Baseline II Visit except Dependence scale for patients from the lead-in study 14861A. This scale will be administered for the first time during the Baseline II Visit of the extension study.

Open-label treatment period with memantine (substudy):
- Patient's current living accommodation (question extracted from the Resource Utilisation in Dementia – Lite (RUD-Lite))
- Dependency scale

Assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

9.2.1 EQ-5D-3L (proxy)

The EQ-5D-3L[13] will be completed by the patient's caregiver as a proxy for the patient.

The EQ-5D-3L is a patient-reported assessment designed to measure the patient's wellbeing. It consists of 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a visual analogue scale (VAS) of the overall health state. Each

descriptive item is rated on a 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.

9.2.2 Resource Utilisation in Dementia (RUD) – Lite

The RUD Lite[14] 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 patients 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.

9.2.3 Dependence scale

The Dependence scale[15] is a clinician-rated scale designed to measure dependence as a health outcome measure in Alzheimer's disease. The Dependence scale is a 13-item scale with questions on social and occupational functioning. Two questions are rated by frequency (*No, Occasionally, Frequently*) and the remaining questions have yes or no responses. The answers are used to derive a dependence level from 0 (*no dependence*) to 5 (*complete dependence*). The clinician interviews an informant who lives with or is well-informed about the patient's day to-day activities. The Dependence scale can be rated by a clinician after a short training session. It takes approximately 15 minutes to complete the scale.

In this study the informant will be the patient's caregiver.

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

9.3 Pharmacokinetic Assessments

Applicable only to open-label treatment period with memantine (substudy):

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 idalopirdine as well as for memantine using analytical methods validated according to the *FDA Guidance for Industry*[16] and the *EMA Guideline on bioanalytical method validation*.[17]

The bioanalysis will be performed by the Department of Bioanalysis, H. Lundbeck A/S. A bioanalytical protocol will be prepared by Lundbeck prior to initiation of the bioanalysis of the blood samples. If other metabolites are identified and considered significant, these may be included in an exploratory analysis.

Selected samples will be subjected to incur sample re-analysis (ISR) as part of the in-study method validation of the applied bioanalytical method. PK results and ISR results will be clearly distinguished from each other in the bioanalytical study report that will be prepared by the Department of Bioanalysis, H. Lundbeck A/S.

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

9.4 Safety Assessments

9.4.1 Adverse Events

The patients will be asked a non-leading question (for example, “how do you feel?”, “how have you felt since your last visit?”) at each visit. 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 10 for further information on adverse events.

9.4.2 Clinical Safety Laboratory Tests

Blood and urine sampling results for clinical safety laboratory tests performed at Visit 7 (Completion Visit) of the lead-in study will be transferred and considered as the Baseline II Visit results.

For patients continuing into the open-label treatment period with memantine (substudy), assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

The clinical safety laboratory tests are listed in Panel 5.

Panel 5 Clinical Safety Laboratory Tests

Haematology 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	**Liver**[a] 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)	**Urine**[b] U-protein U-glucose
		U-blood U-ketones
		Coagulation P-INR aPTT
Lipids[a] S-cholesterol (total) S-triglycerides (non fasting)	**Electrolytes**[a] S-sodium S-potassium S-hydrogencarbonation(HC03-) S-calcium (total)	
Infection S-C-reactive protein (CRP)	**Metabolic**[a] S-albumin S-glucose (non fasting)	
	Kidney[a] S-creatinine S-urea nitrogen (BUN)	
B – blood; P – plasma; S – serum; U – urine		

a Clinical chemistry

b Microscopic examination (leukocytes, erythrocytes and casts) will be performed only if any of the urine evaluations are abnormal.

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

The blood samples will be analysed at the central laboratory specified in Appendix III.

Urine samples will be collected and analysed at the central laboratory specified in Appendix III.

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 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. 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 I values or a diagnosis has been established (see section 8.7). The results must be recorded in the eCRF until the end of the study (see section 8.7).

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, γGT) 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 follow-up laboratory tests should preferably be taken at site and processed in 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.

9.4.3 Vital Signs

Please refer to Panel 2 and Panel 3 for time-points of assessments.

Assessments done at Visit 7 (Completion Visit) of the lead-in study will be transferred and considered as the Baseline II Visit results.

For patients continuing into the open-label treatment period with memantine (substudy), assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

Blood pressure (BP) 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. BP 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.*

9.4.4 Weight

Assessment done at Visit 7 (Completion Visit) of the lead-in study will be transferred and considered as the Baseline II Visit result.

For patients continuing into the open-label treatment period with memantine (substudy), assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

The 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*.

9.4.5 Electrocardiograms (ECGs)

Assessment done at Visit 7 (Completion Visit) of the lead-in study will be transferred and considered as the Baseline II Visit result.

For patients continuing into the open-label treatment period with memantine (substudy), assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

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 as specified in Panel 2 and Panel 3. 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 10 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*.

9.4.6 Physical and Neurological Examinations

The physical and neurological examinations done at Visit 7 (Completion Visit) in the lead-in study will be transferred and considered as the Baseline II Visit results.

For patients continuing into the open-label treatment period with memantine (substudy), assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

The physical examination 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 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*.

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.

9.4.7 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS[18] done at Visit 7 (Completion Visit) of the lead-in study will be transferred and will not be repeated at the Baseline II Visit.

For patients continuing into the open-label treatment period with memantine (substudy), assessments and procedures done at Visit 6 in the open-label treatment period (initial 28-week period) are the same as the Baseline III Visit.

The C-SSRS 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 ”Since last visit” version will be used at all visits. An experienced clinician can use the CSSRS 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.

Only raters who have been trained and certified are allowed to rate patients in study 14861B. The documentation of training issued during the lead-in study covers the extension study 14861B and no additional documentation will be re-issued for existing raters.

New raters joining the study will be trained and certified by ePharmaSolutions using the same certification procedure as in the lead-in study. For each individual patient, the same certified rater should rate the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study.

Exceptional situations must be discussed and approved by the Scales Manager.

9.5 Total Volume of Blood Drawn and Destruction of Blood

Open-label treatment period (initial 28-week period):

The total volume of blood drawn from each patient will be approximately 41 mL 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 will be destroyed after completion of the analysis.

Open-label treatment period with memantine (substudy):

The total volume of blood drawn from each patient will be approximately 84 mL during the study, which includes 41 mL from the open-label treatment period (initial 28-week period) and 43 mL from the open-label treatment period with memantine (substudy).

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

The blood samples will be destroyed after completion of the analysis.

The blood sampling for idalopirdine and memantine will be retained at the bioanalytical facility until the results have been reported. The samples will subsequently be destroyed by the responsible analytical laboratory. The bioanalytical lab will retain the samples until the bioanalytical report is final and no longer than 1 year from last patient last visit. Lundbeck will be notified that the samples are to be destroyed, and the documentation for sample destruction will be kept in the bioanalytical study file.

9.6 Patient Compliance

Responsible study personnel will dispense wallet cards containing IMP (idalopirdine) and donepezil hydrochloride. Additionally, for patients participating in the open-label treatment period with memantine (substudy), memantine will be prescribed according to investigator judgement. Accountability and compliance verification should be documented in the patient's source documents and verified by the Clinical Research Associate (CRA) during monitoring. Patients must be counselled at each visit on the importance of taking the IMP, donepezil and memantine as directed.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[19]

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*[1], 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).

10.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

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

- *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 is not relevant.

Assessment of Outcome

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

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

10.2 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.

10.3 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 intensity changes during the course of the adverse event, this must be recorded on the *AE Intensity Log*.

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 10.4).

Adverse events, including clinically significant out-of-range 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.

10.4 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 *Serious Adverse Event eCRF Form* 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

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 procedures and timelines as those 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*[20] 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.

Lundbeck will assume responsibility for familiarising itself with local requirements regarding reporting SAEs to the IEC or IRB and acting accordingly.

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

10.5 Treatment and Follow-up of Adverse Events

Patients with adverse events 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, 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 tests (see section 9.4.2).

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.

Patients with clinically significant clinical laboratory values at the Completion or Withdrawal Visit must be followed in accordance with usual clinical practice and be scheduled for a Safety Follow-up Visit to allow for a medical examination and/or blood sampling (see section 8.5).

Patients who withdrew due to elevated AST or ALT values (see section 5.4) must be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, INR) should be considered. A gastroenterology or hepatology consultation should also be considered.

10.6 Study Monitoring Committees

10.6.1 Data Monitoring Committee

The DMC consists of specialists within relevant therapeutic areas. The DMC ensures that the ethical principles are observed and monitors the safety of the patients. The DMC will be

informed to what extent the data and analyses provided to them have been quality controlled. Members of the DMC will not be involved in other study-related tasks. The DMC procedures are described in the *Data Monitoring Committee Charter*.

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 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 11.1.3.

The eCRFs use third party software (Rave®) to capture data via an on-line system on a computer. Data related to the study will be recorded electronically in 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 a delegate.

11.1.2 Patient Binders

11.1.2.1 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.

11.1.2.2 Rating Scales and Caregiver Outcome

The *Patient Binder* contains paper versions of the rating 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 the entries in the *Scale* Section are accurate and correct by signing and dating the relevant pages.

Caregiver's response cannot be corrected by the site staff.

11.1.2.3 Serious Adverse Event Fallback Forms

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

11.1.3 External Data

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

The clinical safety laboratory results will be transferred by Quintiles Laboratories.

ECG results will be transferred by Quintiles Cardiac Safety Services.

11.2 Retention of Study Documents at the Site

11.2.1 eCRF Data

If a site closes before the study has been completed, the investigator will continue to have read-only access to the eCRF. If a site closes after the study has been completed, the investigator will no longer have read access to the eCRF. Instead, each site will be provided with a CD-ROM containing the 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 (for example, 15 years [if required by the applicable regulatory requirements]), it is possible for the investigator to request a new CD-ROM with the data related to the site.

11.2.2 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 is longer.

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

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

12 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 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 IMP accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the site's recruitment rate, and the compliance of the site to the protocol and *Good Clinical Practice*.[3] In addition, the CRA will be available for discussions by telephone.

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

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

13 Audits and Inspections

Authorised personnel from Global Clinical Quality Assurance at Lundbeck 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*[3] and all other relevant regulations.

The patients must be informed that authorised personnel from Lundbeck may wish to review 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 all the 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.

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 IRBs and provide a detailed written explanation. The pertinent regulatory authorities must be informed in accordance with national regulations.

If the risk/benefit analysis changes after the termination of the study, the new evaluation must be provided to the IECs and 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 Statistical Methodology

16.1 Responsibilities

The Department of Biostatistics, H. Lundbeck A/S, will perform the statistical analyses described below.

16.2 Analysis Sets

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

- *all-patients-treated set* (APTS) – all patients who took at least one dose of IMP in the open label treatment period (initial 28-week period).
- *all-patients-treated set 2* (APTS2) – all patients who took at least one dose of both IMP and memantine in the open-label treatment period with memantine (substudy).

Each patient will be classified according to this definition at a Classification Meeting held after all the data have been entered in the study database and verified.

All descriptive statistics and statistical analyses in the open-label treatment period (initial 28-week period) will be based on the APTS, and all analyses in the open-label treatment period

with memantine (substudy) will be based on APTS2. Listings will be based on all patients entering the treatment period.

16.3 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

Descriptive statistics will be presented for each treatment period separately.

Descriptive statistics for efficacy assessments (MMSE, ADAS-Cog, ADCS-ADL_{23}, ADCS-CGIC and NPI), Dependence scale, RUD Lite, and EQ-5D-3L will be presented by visit lead-in study, and treatment group in the lead-in study and in total. For the open-label treatment period (initial 28-week period), data will be presented using data from both the lead-in study and the open-label treatment period (initial 28-week period).

If relevant, individual patient profile plots will be generated for selected variables, using data from both the lead-in study and the extension study.

16.4 Patient Disposition

Patient disposition and reason for withdrawal will be presented by treatment period.

Patient disposition will be summarised by lead-in study, and by treatment group in the lead-in study and in total and include the number of patients who completed and the number of patients who withdrew from the study.

The number of patients who withdraw from the study and primary reason for withdrawal as well as all reasons for withdrawal will be summarised by lead-in study, and treatment group in the lead-in study and in total.

Kaplan-Meier time to withdrawal plots in the open-label treatment period (initial 28-week period) will be generated by lead-in study, and treatment group in the lead-in study and in total.

16.5 Demographics and Other Baseline Characteristics

Demographics (sex, age, race) based on APTS and APTS2 will be summarised by treatment group (placebo or idalopirdine all doses pooled) in the lead-in study and in total.

16.6 Recent and Concomitant Medication

Recent and concomitant medication in each treatment period will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name by treatment group (placebo or idalopirdine all doses pooled) in the lead-in study and in total.

16.7 Exposure

Exposure in each treatment period will be calculated per patient and summarised by treatment group (placebo or idalopirdine all doses pooled) in the lead-in study and in total.

Number and percentage of patients with dose reduction of IMP to 30 mg/day in the open-label treatment period (initial 28-week period) will be calculated by treatment group (placebo or idalopirdine all doses pooled) in the lead-in study and in total.

16.8 Efficacy Analyses

On an exploratory basis, changes from baseline in in the open-label treatment period (initial 28-week period) of ADAS-Cog total score, ADCS-ADL23 total score, NPI total score, NPI individual items, EQ-5D-3L utility score, and EQ-5D-3L VAS score will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. Baseline will be defined as the baseline in the lead-in study. The analyses will be performed by lead-in study. The model for the lead-in studies 14861A and 14862A will include the fixed categorical effects of treatment group in the lead-in study, country, visit, treatment-by-visit interaction, MMSE-stratum (<19, ≥ 19), and MMSE-stratum-by-visit interaction as well as the continuous covariates of baseline score and baseline score-by-visit interaction. In all analyses, an unstructured (co)variance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

ADCS-CGIC will be analysed using the same methodology, using the scores at each visit and the ADCS-CGIC score at baseline in the lead-in study as baseline.

16.9 Safety Analyses

Safety tables will be presented for each treatment period separately by treatment group (placebo or idalopirdine all doses pooled) in the lead-in study, and in total.

16.9.1 Analysis of Adverse Events

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

- *treatment-emergent adverse event* (TEAE) – an adverse event that starts on or after the date of first dose of IMP in the extension study 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 in the lead-in study and in total.

If relevant, incidence and prevalence in the lead-in study and in the open-label treatment period (initial 28-week period) for selected preferred terms will be presented by treatment group in the lead-in study.

16.9.2 Analysis of Other Safety Endpoints

Clinical safety laboratory tests, vital signs, weight and ECG parameters will be summarised by visit and last post baseline assessment in the treatment period. For the open-label treatment period (initial 28-week period), the summaries will be presented using data from both the lead-in study and the open-label treatment period (initial 28-week period).

Potentially clinically significant (PCS) values will be flagged and summarised.

If relevant, individual patient profile plots will be generated for selected parameters, using data from both the lead-in study and the extension study.

C-SSRS will be summarised by visit. For the open-label treatment period (initial 28-week period), the summaries will be presented using data from both the lead-in study and the open-label treatment period (initial 28-week period).

16.9.3 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.

16.10 Interim Analyses

An interim analysis may be performed prior to completion of the study to support a potential regulatory submission.

16.11 Sample Size and Power

Open-label treatment period (initial 28-week period):

Approximately 240 sites are planned in 30-35 countries. The study will include eligible patients who have completed Visit 7 (Completion Visit) of the lead-in studies. Assuming a completion rate of 85% and that approximately 85% of these are eligible and complete the extension study, this results in a total of approximately (3x310 + 3x280) x 85% x 85% ≈ 1280 patients completing this study.

Open-label treatment period with memantine (substudy):

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

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

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

16.12 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 any of the lead-in studies are unblinded.

17 Clinical Study Report and Publications

17.1 Clinical Study Report

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

17.2 Data Ownership

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

17.3 Publications

The results of this study will be submitted for publication.

The primary publication based on this study must be published before any secondary publications are submitted for publication.

Authors of the primary publication must fulfil the criteria defined by the *International Committee of Medical Journal Editors (ICMJE)*.[21]

18 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*.[3]

19 Finance

19.1 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.

19.2 Financial Disclosure

All the 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.

19.3 Equipment

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

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Appendix I

Clinical Study Protocol Authentication and Authorisation

Clinical Study Protocol
Authentication and Authorisation

Study title:	An open-label extension study to evaluate the long-term safety and tolerability of Lu AE58054 as adjunctive treatment to donepezil in patients with mild-moderate Alzheimer's disease
Study No.:	14861B
Edition No.:	3.0
Date of edition:	16 June 2015

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: [redacted]

Clinical research scientist: [redacted]

Head, Biostatistics: [redacted]

Divisional Director, GPV: [redacted]

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: [redacted]

Appendix II

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

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

Disallowed Recent and Concomitant Medication

Drug Class	Details
Any investigational drug	Disallowed throughout the whole study.
AChE inhibitors or cholinergic agonists or antagonists	All AChE inhibitors except donepezil are disallowed. Treatment with donepezil must have been stable at 10 mg/day and 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. 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 during the study.
Anorexics	Disallowed during the study.
Antiacne agents	Disallowed during the study. Agents for topical use are allowed.
Antiarrhythmics	*Open-label treatment period (initial 28-week period):* Flecainide and propafenone disallowed. For other antiarrhythmics dose modifications and initiation of treatment are allowed during the study. As specified in the donepezil SPC precaution should be taken when administering quinidine. *Open-label treatment period with memantine (substudy):* Flecainide, quinidine and propafenone disallowed. For other antiarrhythmics dose modifications and initiation of treatment are allowed during the study. Procainamide is allowed but caution should be exercised according to the memantine *SmPC*.
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.
Anticonvulsants	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 during the study with no modification of the dose. Initiation of treatment during the study is disallowed. All other anti-epileptic agents are disallowed during the study, regardless of the indication.

Drug Class	Details
Antidepressants	Stable treatment with no modification of dose with selective serotonin reuptake inhibitors (SSRIs), venlafaxine, moclobemide and mirtazapine for the duration of the study. Paroxetine and duloxetine should be used with caution. Initiation of treatment not allowed during the study. Trazodone (maximum evening dose of 50 mg) is acceptable if the treatment is stable. Initiation and dose modification are not allowed during the study. Other antidepressants are disallowed. As specified in Section 4.5 of the donepezil *SmPC* precaution should be taken when administering fluoxetine.
Antidiarrhoeal agents	Allowed except opioid-containing agents.
Antifungal agents: Systemic Topical	 Systemic antifungal agents are disallowed during the study. Antifungal agents for topical use are allowed.
Antihistamines	Only fexofenadine, (dex)loratidine and cetirizine allowed throughout the study.
Antihypertensives	Centrally active antihypertensives (such as clonidine, alphamethyldopa, guanidine, gaunfacine, moxonidine) are disallowed. For all other antihypertensives, dose modifications and initiation of treatment are allowed during the study.
Anti-impotence agents	Disallowed during the study.
Antinauseants	Occasional use for up to five consecutive days allowed.
Antineoplastics	Disallowed during the study.
Antiobesity agents	Disallowed during the study.
Anti-parkinson agents (e.g., levodopa, dopamine agonists, COMT inhibitors, amantadine, monoamine oxidase B inhibitors, anticholinergics etc)	Disallowed during the study.
Anti-psoriatic agents	Disallowed during the study. Anti-psoriatic agents for topical use are allowed.
Antipsychotics depot	Disallowed during the study.
Antipsychotics typical	Disallowed during the study.
Antipsychotics atypical	Only treatment with risperidone (maximum 2 mg/day) or quetiapine (maximum 100 mg/day) is 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 as anxiolytic treatment is acceptable, provided the dose remains 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.
Beta-blockers	Precaution should be taken when administering betablockers.
Cough/cold agents	*Open-label treatment period (initial 28-week period):* Only non-opioids and codeine allowed. *Open-label treatment period with memantine (substudy):* Only non-opioids and codeine allowed. Dextromethorphan disallowed.
Diuretics	*Open-label treatment period with memantine (substudy):* Hydrochlorothiazide and triamterene are disallowed.

Drug Class	Details
H2 blocker/proton pump inhibitors	*Open-label treatment period (initial 28-week period):* Dose modifications and initiation of treatment allowed during the study. *Open-label treatment period with memantine (substudy):* Dose modifications and initiation of treatment allowed during the study, but caution should be exercised according to the memantine *SmPC*.
Hormones, including hormone-replacement therapy	Dose modifications and initiation of treatment allowed during the study. Steroids: See separate row.
Hormone suppressants	Dose modifications and initiation of treatment allowed during the study.
Hypoglycaemic agents and Insulin	Dose modifications and initiation of treatment allowed during the study. Rosiglitazone is disallowed.
Hypolipidaemics	Dose modifications and initiation of treatment allowed during the study.
Muscle relaxants	Allowed on a p.r.n. basis (not to exceed 5 consecutive days). As specified in Section 4.5 of the donepezil, rivastigmine and galantamine *SmPC* precaution should be taken when administering neuro-muscular blockers.
NMDA-antagonist (memantine)	*Open-label treatment period (initial 28-week period):* Disallowed during the study. *Open-label treatment period with memantine (substudy):* NMDA receptor antagonists, except for memantine, are disallowed (e.g., amantadine, dextromethorphan, ketamine).
Psychotropic agents, not otherwise specified (including herbal agents)	Disallowed during the study. Gingko Biloba is allowed provided the dose remains fixed during the study.
Sedatives/ hypnotics	Zolpidem, zaleplon, and zopiclone: These selected hypnotics are acceptable provided the dose remains fixed during 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 during the study. Topical and inhalant use allowed before and throughout the study.
Urinary alkalinizers	*Open-label treatment period with memantine (substudy):* Disallowed for patients participating in the open-label treatment period with memantine (substudy) (e.g. carbonic anhydrase inhibitors, sodium bicarbonate)

Appendix III

Non-site Study Personnel and Vendors

Non-site Study Personnel and Vendors

Coordinating Investigator	
[redacted], Prof. Dr.	[redacted] Germany Tel [redacted] E-mail: [redacted]
Clinical Research Organisation (CRO) Responsible for Monitoring	
Quintiles	Quintiles United Kingdom 575 East Swedesford Road Suite 200 Berkshire, RG2 6UU England Tel: +44 (0) 1184 508000 Fax: +44 (0) 1344 708300
Primary contact: Clinical research associate (CRA)	The CRA's contact details are in the investigator TMF.
Sponsor & Sponsor Personnel	
H. Lundbeck A/S	2500 Valby (Copenhagen), Denmark +45 36 30 13 11
International study manager	[redacted] Tel: [redacted]
Medical expert	[redacted] Tel [redacted] E-mail: [redacted]
Vendors	
Central laboratory	Quintiles Global Central Laboratories The Alba Campus Rosebank, Livingston West Lothian, EH54 7EG United Kingdom Tel: +44 1506 81 4000 Fax: +44 1506 81 4199 Quintiles Laboratories Ltd 1600 Terrell Mill Road Suite 100 Marietta, GA 30067 USA Tel: +1 770 373 3500 Fax: +1 770 373 3501

Central ECG Reader	Quintiles Cardiac Safety Services Brigade South Parade, 1st Floor No.10, M.G.Road Bangalore – 560001 INDIA Tel: + 91 80 6799 4917
Rater training and certification. Data monitoring of scales	ePharmaSolutions 625 Ridge Pike Suite E402 Building E Conshohocken PA 19428 USA Tel: +1-800-503-9480
Electronic Data Capture	Medidata Solutions Worldwide 79 Fifth Avenue, 8th Floor New York, New York 10003 USA Tel: +1 212 918 1800 Fax: +1 212 918 1818 E-mail: helpdesk@mdsol.com
IVRS/IWRS	Almac Clinical Technologies 25 Fretz Road Souderton, PA 18964 USA Tel: +1 215 660 8500 Fax: +1 215 660 8620

Appendix IV

Lead-in Study Treatment Designs

Lead-in Study Treatment Designs

Study	IMP	Base treatment
14861A	Idalopirdine (30 mg)	Donepezil hydrochloride (10 mg)
	Idalopirdine (60 mg)	
	PBO	
14862A	Idalopirdine (10 mg)	Donepezil hydrochloride (10 mg)
	Idalopirdine (30 mg)	
	PBO	