EU Clinical Trials Register

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

Summary

EudraCT number	2012-004764-22
Trial protocol	GB EE IT LT PT FI IE HU HR CZ
Global end of trial date	19 December 2016

Results information

Result version number	v1 (current)
This version publication date	04 January 2018
First version publication date	04 January 2018

Trial information

Trial identification

Sponsor protocol code	14862A STARBEAM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02006641
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	lundbeckclinicaltrials@lundbeck.com, H. Lundbeck A/S, lundbeckclinicaltrials@lundbeck.com
Scientific contact	lundbeckclinicaltrials@lundbeck.com, H. Lundbeck A/S, lundbeckclinicaltrials@lundbeck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2016
Global end of trial reached?	Yes
Global end of trial date	19 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996)

Background therapy:

The study consisted of a screening period (up to 2-week period from screening to randomization), a 24-week double-blind treatment period with placebo or idalopirdine 10 mg/day or 30 mg/day as adjunctive therapy to donepezil 10 mg/day, and a 4-week safety follow-up period following study completion or withdrawal from treatment.

Evidence for comparator: -

Actual start date of recruitment	14 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 88
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	United Kingdom: 83
Country: Number of subjects enrolled	Croatia: 16
Country: Number of subjects enrolled	Czech Republic: 48
Country: Number of subjects enrolled	Estonia: 51
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 66
Country: Number of subjects enrolled	Lithuania: 45
Country: Number of subjects enrolled	Argentina: 74
Country: Number of subjects enrolled	United States: 165
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Korea, Republic of: 46
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Brazil: 38
Country: Number of subjects enrolled	Israel: 9

Worldwide total number of subjects	858
EEA total number of subjects	477

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	109
From 65 to 84 years	673
85 years and over	76

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo adjunct to 10 mg Donepezil

Placebo: Once daily, matching placebo capsules, orally

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo capsules once daily

Arm title	Idalopirdine 10 mg

Arm description:

Idalopirdine adjunct to 10 mg Donepezil

Idalopirdine: Once daily, encapsulated tablets, orally

Arm type	Experimental
Investigational medicinal product name	Idalopirdine 10 mg
Investigational medicinal product code	
Other name	Lu AE58054
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Encapsulated tablets 10 mg, once daily

Arm title	Idalopirdine 30 mg

Arm description:

Idalopirdine adjunct to 10 mg Donepezil

Idalopirdine: Once daily, encapsulated tablets, orally

Arm type	Experimental

Investigational medicinal product name	Idalopirdine 30 mg
Investigational medicinal product code	
Other name	Lu AE58054
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Encapsulated tablets 30 mg, once daily

Number of subjects in period 1	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg
Started	284	290	284
Completed	258	257	248
Not completed	26	33	36
Caregiver impossibility	-	-	1
protocol non-compliance	-	-	1
Patient has moved	1	-	1
Hospitalisation	-	1	-
Patient's wife died	-	-	1
Withdrawal before treatment	2	5	3
Consent withdrawn by subject	7	12	11
Adverse event, non-fatal	15	11	15
Patient did not want to come	-	-	1
Caregiver in hospital	-	1	-
Patient did not show up	1	-	-
Lost to follow-up	-	1	-
Protocol deviation	-	2	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	858	858	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	109	109	
From 65-84 years	673	673	
85 years and over	76	76	
Age continuous			
Units: years			
arithmetic mean	74.5		
standard deviation	± 81.7	-	
Gender categorical			
Units: Subjects			
Female	527	527	
Male	331	331	
Race			
Units: Subjects			
Asian	70	70	
Black or African American	16	16	
White	750	750	
Unknown or Not Reported	22	22	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo adjunct to 10 mg Donepezil	
Placebo: Once daily, matching placebo capsules, orally	
Reporting group title	Idalopirdine 10 mg
Reporting group description:	
Idalopirdine adjunct to 10 mg Donepezil	
Idalopirdine: Once daily, encapsulated tablets, orally	
Reporting group title	Idalopirdine 30 mg
Reporting group description:	
Idalopirdine adjunct to 10 mg Donepezil	
Idalopirdine: Once daily, encapsulated tablets, orally	

Primary: Change in Cognition

End point title	Change in Cognition
End point description:	

Change from baseline to Week 24 in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) total score.
The Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-cog) is a 11-item neuropsychological test that assess the severity of cognitive impairment. The items determine the patient's orientation, memory, language, and praxis. Total score of the 11 items range from 0 to 70 (lower score indicates lower cognitive impairment).

End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	282	275	
Units: units on a scale				
least squares mean (standard error)	0.64 (± 0.39)	0.55 (± 0.39)	1.27 (± 0.39)	

Statistical analyses

Statistical analysis title	Superiority: Placebo vs idalopirdine 10 mg
Statistical analysis description:	

For demonstrating efficacy of a dose, change in cognition (ADAS-cog) and either change in daily functioning (ADCS-ADL23) or change in global clinical impression (ADCS-CGIC) at Week 24 had to show statistically significant favourable differences compared to placebo at Week 24. Overall, type 1 error was controlled at 5% by multiplicity adjustment. Testing of the doses was done in a gated manner, first testing 30 mg at a 5% significance level, and only if found efficacious, then moving on to 10 mg.

Comparison groups	Idalopirdine 10 mg v Placebo
Number of subjects included in analysis	560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.51

Notes:

[1] - Corrected for multiplicity according to the multiple testing procedure

Statistical analysis title	Superiority Placebo vs idalopirdine 30 mg

Statistical analysis description:

For demonstrating efficacy of a dose, change in cognition (ADAS-cog) and either change in daily functioning (ADCS-ADL23) or change in global clinical impression (ADCS-CGIC) at Week 24 had to show statistically significant favourable differences compared to placebo at Week 24. Overall, type 1 error was controlled at 5% by multiplicity adjustment. Testing of the doses was done in a gated manner, first testing 30 mg at a 5% significance level, and only if found efficacious, then moving on to 10 mg.

Comparison groups	Placebo v Idalopirdine 30 mg
Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2223 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	1.65
Variability estimate	Standard error of the mean
Dispersion value	0.52

Notes:

[2] - Corrected for multiplicity according to the multiple testing procedure

Secondary: Change in daily functioning

End point title	Change in daily functioning

End point description:

Change from baseline to Week 24 in Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL23) total score.
The Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL23) is a 23-item clinician-rated inventory to assess activities of daily living (conducted with a caregiver or informant). Each item comprises a series of hierarchical sub-questions, ranging from the highest level of independent performance to a complete loss for each activity. Total score of the 23 items ranges from 0 to 78 (higher score indicates lower disability).

End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	282	275	
Units: units on a scale				
least squares mean (standard error)	-1.39 (± 0.49)	-1.22 (± 0.49)	-1.36 (± 0.49)	

Statistical analyses

Statistical analysis title	Superiority: Placebo vs idalopirdine 10 mg
Statistical analysis description:	

For demonstrating efficacy of a dose, change in cognition (ADAS-cog) and either change in daily functioning (ADCS-ADL23) or change in global clinical impression (ADCS-CGIC) at Week 24 had to show statistically significant favourable differences compared to placebo at Week 24. Overall, type 1 error was controlled at 5% by multiplicity adjustment. Testing of the doses was done in a gated manner, first testing 30 mg at a 5% significance level, and only if found efficacious, then moving on to 10 mg.

Comparison groups	Placebo v Idalopirdine 10 mg
Number of subjects included in analysis	560
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	1.46
Variability estimate	Standard error of the mean
Dispersion value	0.65

Notes:

[3] - Corrected for multiplicity according to the multiple testing procedure

Statistical analysis title	Superiority: Placebo vs idalopirdine 30 mg
Statistical analysis description:	

For demonstrating efficacy of a dose, change in cognition (ADAS-cog) and either change in daily functioning (ADCS-ADL23) or change in global clinical impression (ADCS-CGIC) at Week 24 had to show statistically significant favourable differences compared to placebo at Week 24. Overall, type 1 error was controlled at 5% by multiplicity adjustment. Testing of the doses was done in a gated manner, first testing 30 mg at a 5% significance level, and only if found efficacious, then moving on to 10 mg.

Comparison groups	Placebo v Idalopirdine 30 mg

Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	1.33
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[4] - Corrected for multiplicity according to the multiple testing procedure

Secondary: Change in global impression

End point title	Change in global impression

End point description:

Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) score at Week 24.
The Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change is a semi-structured interview to assess clinically relevant changes in patients with AD. The items determine cognition, behavior, social and daily functioning. Severity at baseline is rated on a 7-point scale from 1 (normal, not ill at all) to 7 (among the most extremely ill patients). The clinically relevant change from baseline is rated on a 7-point scale from 1 (marked improvement) to 7 (marked worsening).

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	277	282	275	
Units: units on a scale				
least squares mean (standard error)	4.30 (± 0.06)	4.24 (± 0.06)	4.35 (± 0.06)	

Statistical analyses

Statistical analysis title	Superiority: Placebo vs idalopirdine 10 mg

Statistical analysis description:

For demonstrating efficacy of a dose, change in cognition (ADAS-cog) and either change in daily functioning (ADCS-ADL23) or change in global clinical impression (ADCS-CGIC) at Week 24 had to show statistically significant favourable differences compared to placebo at Week 24. Overall, type 1 error was controlled at 5% by multiplicity adjustment. Testing of the doses was done in a gated manner, first testing 30 mg at a 5% significance level, and only if found efficacious, then moving on to 10 mg.

Comparison groups	Placebo v Idalopirdine 10 mg

Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.08

Notes:

[5] - Corrected for multiplicity according to the multiple testing procedure

Statistical analysis title	Superiority: Placebo vs idalopirdine 30 mg

Statistical analysis description:

For demonstrating efficacy of a dose, change in cognition (ADAS-cog) and either change in daily functioning (ADCS-ADL23) or change in global clinical impression (ADCS-CGIC) at Week 24 had to show statistically significant favourable differences compared to placebo at Week 24. Overall, type 1 error was controlled at 5% by multiplicity adjustment. Testing of the doses was done in a gated manner, first testing 30 mg at a 5% significance level, and only if found efficacious, then moving on to 10 mg.

Comparison groups	Placebo v Idalopirdine 30 mg
Number of subjects included in analysis	552
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[6] - Corrected for multiplicity according to the multiple testing procedure

Secondary: Change in behavioural disturbance

End point title	Change in behavioural disturbance

End point description:

Change from baseline to Week 24 in Neuropsychiatric Inventory (NPI) total score.

The Neuropsychiatric Inventory is a 12-item structured interview with a caregiver to assess behavioural disturbances. The NPI comprises 10 behavioural and 2 neurovegetative items. Each item consists of a screening question and several sub-questions that are rated no (not present) or yes (present). Each item is rated for frequency (a 4-point scale from 1 [occasionally] to 4 [very frequent]) and severity (a 3-point scale from 1 [mild] to 3 [marked]). The total NPI score is the frequency ratings multiplied by the severity ratings and ranges from 0 to 144 (higher score indicates worse outcome).

End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	282	275	
Units: units on a scale				
least squares mean (standard error)	-0.31 (± 0.59)	-0.94 (± 0.59)	-0.54 (± 0.60)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Individual Behavioural Disturbance Items

End point title	Change in Individual Behavioural Disturbance Items
End point description:	

Change in single NPI item scores at Week 24.

The Neuropsychiatric Inventory is a 12-item structured interview with a caregiver to assess behavioural disturbances. The NPI comprises 10 behavioural and 2 neurovegetative items. Each item consists of a screening question and several sub-questions that 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 frequent]) and severity (a 3-point scale from 1 [mild] to 3 [marked]). Total score for each single NPI item ranges from 0-12 (frequency multiplied by severity), where higher scores represent worse outcome.

End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	278	282	275	
Units: units on a scale				
least squares mean (standard error)				
Delusions	0.01 (± 0.08)	-0.18 (± 0.08)	0.00 (± 0.08)	
Hallucinations	0.00 (± 0.04)	-0.06 (± 0.04)	-0.03 (± 0.04)	
Agitation/aggression	0.02 (± 0.11)	-0.06 (± 0.11)	-0.06 (± 0.11)	
Depression/dysphoria	-0.20 (± 0.10)	-0.08 (± 0.10)	-0.14 (± 0.10)	
Anxiety	-0.05 (± 0.11)	-0.06 (± 0.11)	-0.02 (± 0.11)	
Elation/euphoria	0.01 (± 0.04)	-0.05 (± 0.04)	-0.02 (± 0.04)	
Apathy/indifference	0.00 (± 0.17)	-0.19 (± 0.17)	-0.24 (± 0.17)	
Disinhibition	0.08 (± 0.09)	0.04 (± 0.09)	0.02 (± 0.09)	
Irritability/lability	0.03 (± 0.12)	-0.05 (± 0.12)	-0.17 (± 0.12)	
Aberrant motor behaviour	-0.03 (± 0.14)	0.06 (± 0.14)	0.12 (± 0.14)	

Sleep	-0.04 (± 0.12)	-0.07 (± 0.12)	0.12 (± 0.12)
Appetite/eating disorder	-0.14 (± 0.14)	-0.30 (± 0.14)	-0.07 (± 0.14)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NPI anxiety item score in patients with an NPI anxiety item score of at least 2 at baseline

End point title	Change in NPI anxiety item score in patients with an NPI anxiety item score of at least 2 at baseline

End point description:

Change from baseline to Week 24 in NPI anxiety item score in patients with an NPI anxiety item score of at least 2 at baseline

The Neuropsychiatric Inventory is a 12-item structured interview with a caregiver to assess behavioural disturbances. The NPI comprises 10 behavioural and 2 neurovegetative items. Each item consists of a screening question and several sub-questions that 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 frequent]) and severity (a 3-point scale from 1 [mild] to 3 [marked]). The total score for the NPI anxiety item ranges from 0-12 (frequency multiplied by severity), where a higher score represents a worse outcome.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	71	56	61	
Units: units on a scale				
least squares mean (standard error)	-1.48 (± 0.38)	-1.82 (± 0.40)	-1.69 (± 0.40)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Improvement

End point title	Clinical Improvement

End point description:

Clinical response at Week 24 (based on pre-specified ADAS-cog, ADCS-ADL23, and ADCS-CGIC changes [change in ADAS-cog below or equal to -4, change in ADCS-ADL23 at least 0, and ADCS-CGIC below or equal to 4])

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	255	257	249	
Units: Count of participants				
number (not applicable)	20	33	22	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Worsening

End point title	Clinical Worsening

End point description:

Clinical worsening at Week 24 (Based on pre-specified ADAS-cog, ADCS-ADL23, and ADCS-CGIC changes [change in ADAS-cog above or equal to 4, change in ADCS-ADL23 below 0, and ADCS-CGIC above 4])

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	255	257	249	
Units: Count of participants	27	28	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cognitive aspects of mental function

End point title	Change in cognitive aspects of mental function

End point description:

Change from baseline to Week 24 in Mini Mental State Examination (MMSE).
The Mini Mental State Examination (MMSE) is an 11-item test to assess the cognitive aspects of mental function. The subtests assess orientation, memory, attention, language, and visual construction. The scores for each item is dichotomous (1 = response is correct, 0 = response is incorrect). Total score of the 11 items ranges from 0 to 30 (higher score indicates lower deficit).

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	258	257	248	
Units: Units on a scale				
least squares mean (standard error)	-0.24 (± 0.21)	-0.45 (± 0.21)	-0.34 (± 0.21)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in health-related quality of life (EQ-5D) utility score

End point title	Change in health-related quality of life (EQ-5D) utility score

End point description:

Change from baseline to Week 24 in EuroQol 5-dimensional (EQ-5D) utility score

The EQ-5D is a patient-reported assessment that measures the patient's well-being. It consists of an utility score based on 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and depression/anxiety) and a Visual Analogue Scale (VAS). Each descriptive item is rated on a 3-point index ranging from 1 (no problems) to 3 (extreme problems) that is used for calculating a single summary index (from 0 to 1). A higher EQ-5D score indicates a worse outcome.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	274	275	266	
Units: units on a scale				
least squares mean (standard error)	0.03 (± 0.01)	0.02 (± 0.01)	0.01 (± 0.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in health-related quality of life (EQ-5D VAS)

End point title	Change in health-related quality of life (EQ-5D VAS)

End point description:

Change from baseline to Week 24 in EQ-5D Visual Analogue Scale (EQ-5D VAS).

The EQ-5D is a patient-reported assessment that measures the patient's well-being. It consists of an utility score based on 5 descriptive items (mobility, self-care, usual activities, pain/discomfort, and

depression/anxiety) and a Visual Analogue Scale (VAS). The VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Idalopirdine 10 mg	Idalopirdine 30 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	274	274	266	
Units: Units on a scale				
least squares mean (standard error)	1.35 (± 0.99)	1.87 (± 0.99)	1.00 (± 1.01)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
First dose to end of study (week 28)	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo adjunct to 10 mg Donepezil	
Reporting group title	Idalopirdine 30 mg
Reporting group description:	
Idalopirdine adjunct to 10 mg Donapezile	
Reporting group title	Idalopirdine 10 mg
Reporting group description:	
Idalopirdine adjunct to 10 mg Donepezile	

Serious adverse events	Placebo	Idalopirdine 30 mg	Idalopirdine 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 282 (4.26%)	15 / 281 (5.34%)	13 / 285 (4.56%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anal cancer			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed[1]	0 / 101 (0.00%)	1 / 112 (0.89%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Laryngeal haemorrhage			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	2 / 282 (0.71%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressive symptom			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucinations, mixed			

subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac arrest			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 282 (0.00%)	2 / 281 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid sinus syndrome			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	2 / 285 (0.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

	subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke				
	subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	1 / 285 (0.35%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope				
	subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack				
	subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders				
Lymphadenitis				
	subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders				
Dysphagia				
	subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease				
	subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia				
	subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis				

subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 282 (0.00%)	1 / 281 (0.36%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 282 (0.35%)	0 / 281 (0.00%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	0 / 282 (0.00%)	2 / 281 (0.71%)	0 / 285 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 282 (0.00%)	0 / 281 (0.00%)	1 / 285 (0.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This Serious Adverse Event is only applicable for male subjects.

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Idalopirdine 30 mg	Idalopirdine 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 282 (11.70%)	31 / 281 (11.03%)	26 / 285 (9.12%)
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	33 / 282 (11.70%)	31 / 281 (11.03%)	26 / 285 (9.12%)
occurrences (all)	71	65	52

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2014	Protocol Amendment PA01: To allow re-screening of patients, changes of eligibility criteria and to provide clarifications where needed. Major Changes: Safety Follow-up visit window: this was defined as up to 7 days for patients who withdrew. Visits taking place over 2 consecutive days: it was clarified that IMP had to be dispensed on the second day, after all assessments were performed. Drop-out Retrieval Visit: it was clarified that only new SAEs which were considered as possibly/probably related to IMP by the investigator were to be reported. Screening period: it was clarified that this need not necessarily be a 2-week period, but that it could be up to 2 weeks. Safety follow-up of patients who withdraw consent: it was clarified that such patients had to have a safety follow-up visit, but that the visit was only to be recorded in the medical records. Exclusion criterion 17: it was clarified that patients with pacemakers were eligible provided they followed a routine check-up with their doctor and were considered stable. Exclusion criterion 28: the exclusion criteria for heart rate and the duration of the PR interval were revised. Re-screening: the possibility of re-screening patients, who failed screening due to certain treatable medical conditions, but who were otherwise eligible was added. MMSE: it was clarified that at the Screening visit, this was to be performed prior to any of the other assessments, including ADAS-Cog. SAEs: it was added that under no circumstance were investigators to report SAEs to Lundbeck beyond 24 hours. Concomitant medication: clarifications on the use of other investigational drugs, selected anticonvulsants, and trazodone were provided.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: