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

Summary

EudraCT number	2012-004763-45
Trial protocol	CZ IT BE DE DK BG ES
Global end of trial date	19 July 2016

Results information

Result version number	v1 (current)
This version publication date	04 August 2017
First version publication date	04 August 2017

Trial information

Trial identification

Sponsor protocol code	14861A STARSHINE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01955161
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9 Valby, Denmark, , 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 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 July 2016
Global end of trial reached?	Yes
Global end of trial date	19 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish efficacy of idalopirdine (Lu AE58054) as adjunctive therapy to donepezil for symptomatic treatment of patients with mild-moderate Alzheimer’s disease

Protection of trial subjects:

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

Background therapy:

Donezepil

Evidence for comparator: -

Actual start date of recruitment	09 October 2013
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: 73
Country: Number of subjects enrolled	Spain: 60
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Bulgaria: 60
Country: Number of subjects enrolled	Czech Republic: 109
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 59
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	Argentina: 70
Country: Number of subjects enrolled	Chile: 90
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Ukraine: 61
Country: Number of subjects enrolled	United States: 130
Country: Number of subjects enrolled	South Africa: 57
Worldwide total number of subjects	933
EEA total number of subjects	485

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)	143
From 65 to 84 years	704
85 years and over	86

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	Subject, Investigator

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 30 mg

Arm description:

Idalopirdine adjunct to 10 mg Donepezil

Idalopirdine: Once daily, encapsulated tablets, orally

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

Dosage and administration details:

Encapsulated tables 30 mg, once daily

Arm title	Idalopirdine 60 mg

Arm description:

Idalopirdine adjunct to 10 mg Donepezil Idalopirdine: Once daily, encapsulated tablets, orally

Arm type	Experimental

Investigational medicinal product name	Idaloprirdine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Encapsulated tablets 60 mg, once daily

Number of subjects in period 1	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg
Started	310	313	310
Completed	283	288	275
Not completed	27	25	35
Adverse event, serious fatal	1	1	3
Other reason: caregiver unavailable	1	-	-
Consent withdrawn by subject	9	8	12
Other reason: moved to nursing home	-	1	-
Other reason: physician decision	-	1	1
Adverse event, non-fatal	10	14	15
Other reason: insufficient compliance	-	-	1
Other reason: disallowed medication	1	-	1
Other reason: patient's will	-	-	1
Withdrawal before treatment	2	-	1
Other reason: primary biliary cirrhosis	1	-	-
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	933	933	
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)	143	143	
From 65-84 years	704	704	
85 years and over	86	86	
Age continuous Units: years			
arithmetic mean	73.8		
standard deviation	± 8.5	-	
Gender categorical Units: Subjects			
Female	608	608	
Male	325	325	
Race Units: Subjects			
Asian	5	5	
Native Hawaiian or Other Pacific Islander	3	3	
Black or African American	8	8	
White	857	857	
Unknown or Not Reported	60	60	

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 30 mg

Reporting group description:

Idalopirdine adjunct to 10 mg Donepezil

Idalopirdine: Once daily, encapsulated tablets, orally

Reporting group title	Idalopirdine 60 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 to Week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	310	308	
Units: Unit on a scale				
least squares mean (standard error)	0.13 (± 0.35)	0.47 (± 0.35)	0.18 (± 0.35)	

Statistical analyses

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) had to show statistically significant favourable differences compared to placebo at Week 24. Multiple testing procedures were used to control the overall type 1 error at 5%. The null hypothesis of no difference in mean change from baseline in ADAS-cog total score at Week 24 was tested for each dose at significance level 2.5%

Comparison groups	Placebo v Idalopirdine 30 mg

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9591 [1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	1.26
Variability estimate	Standard error of the mean
Dispersion value	0.47

Notes:

[1] - Corrected for multiplicity

Statistical analysis title	Superiority: Placebo vs. idalopirdine 60 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) had to show statistically significant favourable differences compared to placebo at Week 24. Multiple testing procedures were used to control the overall type 1 error at 5%. The null hypothesis of no difference in mean change from baseline in ADAS-cog total score at Week 24 was tested for each dose at significance level 2.5%.

Comparison groups	Placebo v Idalopirdine 60 mg
Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.98
Variability estimate	Standard error of the mean
Dispersion value	0.47

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 to week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	310	308	
Units: Units on a scale				
least squares mean (standard error)	-2.03 (± 0.49)	-2.12 (± 0.48)	-2.02 (± 0.49)	

Statistical analyses

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) had to show statistically significant favourable differences compared to placebo at Week 24. Multiple testing procedures were used to control the overall type 1 error at 5%. The null hypothesis of no difference in mean change from baseline in ADAS-cog total score at Week 24 was tested for each dose at significance level 2.5%.

Comparison groups	Placebo v Idalopirdine 30 mg
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

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

Statistical analysis title	Superiority: Placebo vs. idalopirdine 60 mg
Comparison groups	Placebo v Idalopirdine 60 mg
Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 1 [5]
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	1.31
Variability estimate	Standard error of the mean
Dispersion value	0.66

Notes:

[4] - 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) had to show statistically significant favourable differences compared to placebo at Week 24. Multiple testing procedures were used to control the overall type 1 error at 5%. The null hypothesis of no difference in mean change from baseline in ADAS-cog total score at Week 24 was tested for each dose at significance level 2.5%.
[5] - 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

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	303	309	307	
Units: Units on a scale				
least squares mean (standard error)	4.29 (± 0.07)	4.32 (± 0.07)	4.13 (± 0.07)	

Statistical analyses

Statistical analysis title	Superiority: Placebo vs. idalopirdine 30 mg

Statistical analysis description:

For demonstrating efficacy of a dose, ADAS-cog total score and either ADCS-ADL23 total score or ADCS CGIC had to show statistically significant favourable differences compared to placebo at Week 24. Multiple testing procedures were used to control the overall type 1 error at 5%. The null hypothesis of no difference in mean change from baseline in ADAS-cog total score at Week 24 was tested for each dose at significance level 2.5%.

Comparison groups	Placebo v Idalopirdine 30 mg

Number of subjects included in analysis	612
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

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

Statistical analysis title	Superiority: Placebo vs. idalopirdine 60 mg

Statistical analysis description:

For demonstrating efficacy of a dose, ADAS-cog total score and either ADCS-ADL23 total score or ADCS CGIC had to show statistically significant favourable differences compared to placebo at Week 24. Multiple testing procedures were used to control the overall type 1 error at 5%. The null hypothesis of no difference in mean change from baseline in ADAS-cog total score at Week 24 was tested for each dose at significance level 2.5%.

Comparison groups	Placebo v Idalopirdine 60 mg
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[7] - 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 then rated for frequency (a 4-point scale from 1 [occasionally] to 4 [very frequent]), severity (a 3-point scale from 1 [mild] to 3 [marked]), and caregiver distress (a 5-point scale from 0 [not at all] to 5 [very severely or extremely]). Total score of the frequency ratings multiplied by the severity ratings ranges from 0 to 144 and the total score of the caregiver distress ratings ranges from 0 to 60.

End point type	Secondary
End point timeframe:	
Baseline to week 24	

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	310	308	
Units: Units on a scale				
least squares mean (standard error)	-0.21 (± 0.62)	-0.21 (± 0.62)	-0.39 (± 0.63)	

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]), severity (a 3-point scale from 1 [mild] to 3 [marked]), and caregiver distress (a 5-point scale from 0 [not at all] to 5 [very severely or extremely]). Total score of the frequency ratings multiplied by the severity ratings ranges from 0 to 144 and the total score of the caregiver distress ratings ranges from 0 to 60.

End point type	Secondary
End point timeframe:	
Baseline to week 24	

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	304	310	308	
Units: Units on a scale				
least squares mean (standard error)				
Delusions	-0.11 (± 0.09)	-0.04 (± 0.09)	-0.01 (± 0.09)	
Hallucinations	0.13 (± 0.07)	0.03 (± 0.07)	-0.03 (± 0.07)	
Agitation/agression	0.01 (± 0.11)	0.04 (± 0.11)	0.1 (± 0.11)	
Depression/dysphoria	0.02 (± 0.09)	-0.06 (± 0.09)	-0.08 (± 0.1)	
Anxiety	-0.02 (± 0.11)	-0.13 (± 0.11)	-0.13 (± 0.11)	
Elation/euphoria	0.09 (± 0.05)	0.03 (± 0.05)	0.03 (± 0.05)	
Apathy/indifference	-0.18 (± 0.15)	-0.23 (± 0.15)	-0.27 (± 0.15)	
Disinhibition	0.05 (± 0.08)	-0.06 (± 0.08)	-0.01 (± 0.08)	
Irritability/lability	-0.14 (± 0.12)	0.02 (± 0.12)	0 (± 0.12)	

Aberrant mtor behaviour	0.03 (± 0.12)	0.33 (± 0.12)	-0.13 (± 0.13)	
Sleep	0.03 (± 0.11)	0.01 (± 0.11)	0.03 (± 0.11)	
Appetite/eating disorder	-0.08 (± 0.13)	-0.14 (± 0.13)	-0.04 (± 0.13)	

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:

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, where anxiety is one of the behavioural 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]), severity (a 3-point scale from 1 [mild] to 3 [marked]), and caregiver distress (a 5-point scale from 0 [not at all] to 5 [very severely or extremely]). Total score of the frequency ratings multiplied by the severity ratings ranges from 0 to 144 and the total score of the caregiver distress ratings ranges from 0 to 60.

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	83	76	
Units: Units on a scale				
least squares mean (standard error)	-1.12 (± 0.3)	-1.56 (± 0.3)	-1.64 (± 0.32)	

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 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	284	290	278	
Units: Count of participants	34	37	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical worsening

End point title	Clinical worsening

End point description:

End point type	Secondary

End point timeframe:

Week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	284	290	278	
Units: Count of participants	40	42	33	

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 to week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	282	288	274	
Units: Units on a scale				
least squares mean (standard error)	0.06 (± 0.16)	-0.27 (± 0.16)	0.27 (± 0.17)	

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).

End point type	Secondary

End point timeframe:

Baseline to week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	306	304	
Units: Units on a scale				
least squares mean (standard error)	-0.01 (± 0.01)	0 (± 0.01)	0 (± 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 to week 24

End point values	Placebo	Idalopirdine 30 mg	Idalopirdine 60 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	301	307	304	
Units: Units on scale				
least squares mean (standard error)	-0.4 (± 1.01)	-0.12 (± 1.01)	0.34 (± 1.03)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to end of study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Idalopirdine 60 mg
Reporting group description: -	
Reporting group title	Idalopirdine 30 mg
Reporting group description: -	

Serious adverse events	Placebo	Idalopirdine 60 mg	Idalopirdine 30 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 308 (3.90%)	20 / 309 (6.47%)	18 / 313 (5.75%)
number of deaths (all causes)	1	3	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 308 (0.00%)	2 / 309 (0.65%)	0 / 313 (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
Hypotension			

subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Colostomy closure			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Rehabilitation therapy			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed[1]	0 / 198 (0.00%)	1 / 201 (0.50%)	0 / 208 (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
Vaginal fistula			
subjects affected / exposed[2]	1 / 198 (0.51%)	0 / 201 (0.00%)	0 / 208 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Dyspnoea			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 308 (0.32%)	1 / 309 (0.32%)	0 / 313 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Impulse-control disorder			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Bilirubin conjugated increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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

Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Blood bilirubin increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
C-reactive protein increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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			
Femoral neck fracture			
subjects affected / exposed	1 / 308 (0.32%)	1 / 309 (0.32%)	0 / 313 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Hip fracture			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Radius fracture			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Wrist fracture			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
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 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
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 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Coronary artery disease			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Sinus node dysfunction			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Nervous system disorders			

Cerebral arteriosclerosis			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Cerebral haematoma			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Dementia alzheimer's type			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Presyncope			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 308 (0.32%)	1 / 309 (0.32%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Gastrointestinal disorders			

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Pancreatitis acute			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	2 / 308 (0.65%)	0 / 309 (0.00%)	0 / 313 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (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
Bacterial diarrhoea			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	0 / 308 (0.00%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Pneumonia			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	0 / 313 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	2 / 308 (0.65%)	0 / 309 (0.00%)	0 / 313 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	0 / 313 (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
Urinary tract infection			
subjects affected / exposed	0 / 308 (0.00%)	1 / 309 (0.32%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 308 (0.32%)	0 / 309 (0.00%)	1 / 313 (0.32%)
occurrences causally related to treatment / all	0 / 1	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: Only relevant in woman

[2] - 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: Only relevant in women

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

Non-serious adverse events	Placebo	Idalopirdine 60 mg	Idalopirdine 30 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 308 (12.66%)	49 / 309 (15.86%)	56 / 313 (17.89%)
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 308 (0.32%)	15 / 309 (4.85%)	17 / 313 (5.43%)
occurrences (all)	1	15	17
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	27 / 308 (8.77%)	16 / 309 (5.18%)	27 / 313 (8.63%)
occurrences (all)	52	41	55
Fall			
subjects affected / exposed	15 / 308 (4.87%)	19 / 309 (6.15%)	16 / 313 (5.11%)
occurrences (all)	16	20	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2013	PA01 Before study start The Drop-out Retrieval Visit was added. Analysis of primary and key secondary endpoints: exploratory MMRM analysis pooling the 30 and 60mg doses and testing the effect versus placebo was added. Sensitivity analyses of the primary and key secondary endpoints: MMRM analyses of efficacy data collected at the Withdrawal Follow-up Visit and the Drop-out Retrieval Visit for withdrawn patients were added. A secondary endpoint addressing the secondary objective was added: change from baseline to Week 24 in NPI Anxiety score in patients with an NPI Anxiety score ≥2 at baseline. Analysis of secondary endpoints: changes from baseline in NPI Anxiety score at Weeks 4, 12, and 24 in patients with a score ≥2 at baseline analysed using the same methodology as that described for the primary endpoint were added. The ADAS-cog component of the clinical response definition at Week 24 was redefined from ADAS-cog change <-4 to ADAS-cog change ≤-4 (this change was repeated in PA02). Unblinding procedure: the investigator could break the code immediately if he/she judged it necessary to ensure the safety of the patient, without prior contact to the CRA, was added.
19 February 2014	PA02 After study start The Dependence Scale was added. Exclusion criterion 17: that patients with pacemakers were eligible provided they followed a routine check-up with their doctor and were considered stable was clarified. Exclusion criterion 28: the exclusion criteria for heart rate and the duration of the PR interval were revised. The possibility of re-screening patients who failed screening due to certain treatable medical conditions but who were otherwise eligible was added. Concomitant medication use was clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported