

**Clinical trial results:****Randomised, double-blind, parallel-group, placebo-controlled study of Lu AE58054 in patients with mild-moderate Alzheimer's disease treated with an acetylcholinesterase inhibitor; Study 3****Summary**

EudraCT number	2012-004765-40
Trial protocol	CZ GB DE SK ES
Global end of trial date	12 January 2017

Results information

Result version number	v1 (current)
This version publication date	28 January 2018
First version publication date	28 January 2018

Trial information**Trial identification**

Sponsor protocol code	14863A STARBRIGHT
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02006654
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottliavej 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	12 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2017
Global end of trial reached?	Yes
Global end of trial date	12 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the efficacy of Lu AE58054 as adjunctive therapy to acetylcholinesterase inhibitors (AChEIs) 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 60mg/day as adjunctive therapy to an acetylcholinesterase inhibitor (donepezil 10mg/day, rivastigmine at the patient's individual maintenance dose, or galantamine at the patient's individual maintenance dose), and a 4-week safety follow-up period following study completion or withdrawal from treatment. The dose could be decreased once during the study to 30mg/day if 60mg/day was not well tolerated in the opinion of the investigator. The dose could be increased again to 60mg/day, after which the dose was kept fixed for the remainder of the study. Dose changes were permitted until Week 12 (Visit 5).

Evidence for comparator: -

Actual start date of recruitment	28 February 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	Australia: 42
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Mexico: 48
Country: Number of subjects enrolled	Singapore: 32
Country: Number of subjects enrolled	Serbia: 21
Country: Number of subjects enrolled	Turkey: 32
Country: Number of subjects enrolled	United States: 82
Country: Number of subjects enrolled	Slovakia: 56
Country: Number of subjects enrolled	Spain: 127
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Czech Republic: 79
Country: Number of subjects enrolled	France: 20

Country: Number of subjects enrolled	Germany: 80
Worldwide total number of subjects	734
EEA total number of subjects	373

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)	110
From 65 to 84 years	566
85 years and over	58

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 Comparator: Placebo

Arm description:

Placebo adjunct to base treatment with an AChEI

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:

Once daily, matching placebo capsules, orally

Arm title	Experimental: Idalopirdine 60 mg (or 30 mg)
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Arm description:

Idalopirdine adjunct to base treatment with an AChEI

Arm type	Experimental
Investigational medicinal product name	Idalopirdine 60 mg (or 30 mg)
Investigational medicinal product code	Lu AE58054
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily, encapsulated tablets, orally

Number of subjects in period 1	Placebo Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)
Started	369	365
Completed	324	321
Not completed	45	44
Adverse event, serious fatal	1	-

Insufficient compliance	1	-
patient's will	2	1
Withdrawal before treatment	4	2
Mood disorder	-	1
faecal incontinence	-	1
Consent withdrawn by subject	14	12
Adverse event, non-fatal	16	17
Moving out of state	-	1
Worsening cognitive condition	-	1
disallowed medication	1	-
Lost to follow-up	1	-
Protocol deviation	5	8

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)
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Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	734	734	
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)	110	110	
From 65-84 years	566	566	
85 years and over	58	58	
Age continuous Units: years			
arithmetic mean	73.9		
standard deviation	± 8.3	-	
Gender categorical Units: Subjects			
Female	464	464	
Male	270	270	
Race Units: Subjects			
Asian	79	79	
Black or African American	19	19	
White	594	594	
Unknown or Not Reported	42	42	

End points

End points reporting groups

Reporting group title	Placebo Comparator: Placebo
Reporting group description: Placebo adjunct to base treatment with an AChEI	
Reporting group title	Experimental: Idalopirdine 60 mg (or 30 mg)
Reporting group description: Idalopirdine adjunct to base treatment with an AChEI	

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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	361		
Units: Units on a scale				
least squares mean (standard error)	0.68 (± 0.37)	0.13 (± 0.38)		

Statistical analyses

Statistical analysis title	Change in Cognition
Statistical analysis description: For demonstrating efficacy, 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 idalopirdine at significance level 5%.	
Comparison groups	Placebo Comparator: Placebo v Experimental: Idalopirdine 60 mg (or 30 mg)

Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2365 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	0.36
Variability estimate	Standard error of the mean
Dispersion value	0.46

Notes:

[1] - Corrected for multiplicity

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.	
<p>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).</p>	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	353	357		
Units: Units on a scale				
least squares mean (standard error)	4.32 (± 0.07)	4.39 (± 0.07)		

Statistical analyses

Statistical analysis title	Change in Global Impression
Statistical analysis description:	
<p>For demonstrating efficacy, 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 at significance level 5%.</p>	

Comparison groups	Placebo Comparator: Placebo v Experimental: Idalopirdine 60 mg (or 30 mg)
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4064 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.08

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.	
<p>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).</p>	
End point type	Secondary
End point timeframe:	
Baseline and Week 24	

End point values	Placebo Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	361		
Units: Units on a Scale				
least squares mean (standard error)	-1.72 (± 0.50)	-1.05 (± 0.51)		

Statistical analyses

Statistical analysis title	Change in Daily Functioning
Statistical analysis description:	
For demonstrating efficacy, 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 at significance level 5%.

Comparison groups	Placebo Comparator: Placebo v Experimental: Idalopirdine 60 mg (or 30 mg)
Number of subjects included in analysis	717
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4064 ^[3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.57
upper limit	1.92
Variability estimate	Standard error of the mean
Dispersion value	0.63

Notes:

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

Secondary: Change in Behavioural Disturbance

End point title	Change in Behavioural Disturbance
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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]) 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
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End point timeframe:

Baseline and Week 24

End point values	Placebo Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	361		
Units: Units on a scale				
least squares mean (standard error)	-0.46 (± 0.53)	-0.74 (± 0.54)		

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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	356	361		
Units: Units on a scale				
least squares mean (standard error)				
Delusions	-0.00 (± 0.10)	0.03 (± 0.10)		
Hallucinations	0.05 (± 0.06)	0.08 (± 0.06)		
Agitation/aggression	0.15 (± 0.11)	0.03 (± 0.11)		
Depression/dysphoria	-0.28 (± 0.09)	-0.18 (± 0.09)		
Anxiety	-0.16 (± 0.09)	-0.07 (± 0.09)		
Elation/euphoria	0.02 (± 0.04)	0.03 (± 0.04)		
Apathy/indifference	-0.06 (± 0.15)	-0.19 (± 0.15)		
Disinhibition	0.12 (± 0.08)	-0.00 (± 0.08)		
Irritability/lability	0.10 (± 0.12)	-0.04 (± 0.12)		
Aberrant motor behaviour	0.08 (± 0.11)	0.11 (± 0.11)		
Sleep	-0.13 (± 0.11)	-0.12 (± 0.11)		
Appetite/eating disorder	-0.25 (± 0.12)	-0.21 (± 0.12)		

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
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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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	83		
Units: Units on a scale				
least squares mean (standard error)	-1.93 (± 0.32)	-1.52 (± 0.33)		

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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	321		
Units: Participants	32	35		

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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324	321		
Units: Participants	37	40		

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
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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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	320		
Units: Units on a scale				
least squares mean (standard error)	-0.64 (± 0.20)	-0.35 (± 0.20)		

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
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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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	354		
Units: Units on a scale				
least squares mean (standard error)	-0.01 (± 0.01)	-0.00 (± 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)
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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 Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	351	353		
Units: Units on a scale				
least squares mean (standard error)	-0.40 (± 1.00)	0.51 (± 1.02)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose to follow-up

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo Comparator: Placebo
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Reporting group description:

Placebo adjunct to base treatment with an AChEI

Reporting group title	Experimental: Idalopirdine 60 mg (or 30 mg)
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Reporting group description:

Idalopirdine adjunct to base treatment with an AChEI

Serious adverse events	Placebo Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 365 (6.03%)	28 / 363 (7.71%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 365 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed ^[1]	0 / 234 (0.00%)	1 / 228 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			

subjects affected / exposed	2 / 365 (0.55%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal haemorrhage			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Behavioural and psychiatric symptoms of dementia			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Personality disorder			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram st segment depression			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 365 (0.27%)	5 / 363 (1.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	2 / 365 (0.55%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 365 (0.00%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 365 (0.00%)	2 / 363 (0.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 365 (0.55%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial haematoma			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 365 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Colitis ulcerative			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 365 (0.27%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 365 (0.00%)	1 / 363 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 365 (0.27%)	0 / 363 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	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 Adverse Event is only applicable for female subjects.

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

Non-serious adverse events	Placebo Comparator: Placebo	Experimental: Idalopirdine 60 mg (or 30 mg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 365 (17.53%)	82 / 363 (22.59%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 365 (0.82%)	19 / 363 (5.23%)	
occurrences (all)	3	19	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 365 (0.55%)	22 / 363 (6.06%)	
occurrences (all)	2	22	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	43 / 365 (11.78%)	40 / 363 (11.02%)	
occurrences (all)	71	73	
Fall			
subjects affected / exposed	21 / 365 (5.75%)	19 / 363 (5.23%)	
occurrences (all)	21	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2014	PA01: Deletion of text regarding open-label extension study as it was no longer applicable for the study. 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. Clarification and specifications to the use of concomitant medication.
02 February 2016	PA02: The restriction regarding the number of patients to be included in each of the two base treatment strata was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported