Clinical trial results:
Interventional, randomized, double-blind, active-controlled study of the efficacy of Lu AF35700 in patients with early-in-disease or late-in-disease treatment-resistant schizophrenia

Summary

EudraCT number	2017-000788-34
Trial protocol	BG GB
Global end of trial date	05 February 2019

Results information

Result version number	v1 (current)
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information

Trial identification

Sponsor protocol code	17303A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03230864
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, 0045 36301311, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 0045 36301311, 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	05 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2018
Global end of trial reached?	Yes
Global end of trial date	05 February 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study evaluates the efficacy of 10 mg/day Lu AF35700 on symptoms of schizophrenia in patients with early-in-disease (ED) or late-in-disease (LD) treatment-resistant schizophrenia (TRS)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 July 2017
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	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 44
Country: Number of subjects enrolled	Japan: 9
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	119
EEA total number of subjects	46

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)	116
From 65 to 84 years	3

85 years and over	0

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	Prospective Confirmation (PC) Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	PC Period - Risperidone

Arm description:

Single (patient)-blinded treatment period with risperidone for 6 weeks

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

Dosage and administration details:

4-6 mg/day, encapsulated tablets, orally

Arm title	PC Period - Olanzapine

Arm description:

Single (patient)-blinded treatment period with olanzapine for 6 weeks

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

Dosage and administration details:

15-20 mg/day, encapsulated tablets, orally

Number of subjects in period 1	PC Period - Risperidone	PC Period - Olanzapine
Started	68	51
Completed	36	32
Not completed	32	19
Consent withdrawn by subject	4	1

Adverse event, non-fatal	3	-
Study Personnel Decision	1	-
Sponsor Decision	9	9
Did not fulfill rand criteria DBT	14	5
Protocol deviation	1	2
Lack of efficacy	-	2

Period 2

Period 2 title	Double-blind Treatment (DBT) Period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	DBT, Lu AF35700 10 mg

Arm description:

Eligible patients from PC Period (based on criteria to which invetsigator and patient are blinded), will be randomly assigned (1:1) double-blind treatment in DBT Period, 8 weeks. Lu AF35700: 10 mg/day, encapsulated tablets, orally

Arm type	Experimental
Investigational medicinal product name	Lu AF35700
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lu AF35700 10 mg/day, encapsulated tablets, orally

Arm title	DBT, Continued Treatment

Arm description:

Eligible patients from PC Period (based on crietria to which investigator and patient are blinded), will be randomly assigned (1:1) double-blind treatment in DBT Period, 8 weeks. Patients in this arm will continue with the same treatment and dose as at last visit of PC Period. Risperidone: 4-6 mg/day, encapsulated tablets, orally. Olanzapine: 15-20 mg/day, encapsulated tablets, orally

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

Dosage and administration details:

15-20 mg/day, encapsulated tablets, orally

Investigational medicinal product name	Risperidone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

4-6 mg/day, encapsulated tablets, orally

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: It is correct that not all the patients that enrolled the study started the double bind treatment period which explains that the numbers are not the same.

Number of subjects in period 2[2]	DBT, Lu AF35700 10 mg	DBT, Continued Treatment
Started	35	33
Completed	27	31
Not completed	8	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	5	1
Sponsor Decision	2	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: It is correct that not all the patients that enrolled the study started the double bind treatment period which explains that the numbers are not the same.

Baseline characteristics

Reporting groups	
Reporting group title	DBT, Lu AF35700 10 mg
Reporting group description:	
Eligible patients from PC Period (based on criteria to which invetsigator and patient are blinded), will be randomly assigned (1:1) double-blind treatment in DBT Period, 8 weeks. Lu AF35700: 10 mg/day, encapsulated tablets, orally	
Reporting group title	DBT, Continued Treatment
Reporting group description:	
Eligible patients from PC Period (based on crietria to which investigator and patient are blinded), will be randomly assigned (1:1) double-blind treatment in DBT Period, 8 weeks. Patients in this arm will continue with the same treatment and dose as at last visit of PC Period. Risperidone: 4-6 mg/day, encapsulated tablets, orally. Olanzapine: 15-20 mg/day, encapsulated tablets, orally	

Reporting group values	DBT, Lu AF35700 10 mg	DBT, Continued Treatment	Total
Number of subjects	35	33	68
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	42.9	42	
standard deviation	± 11.26	± 12.26	-
Gender categorical			
Units: Subjects			
Female	15	17	32
Male	20	16	36
Race			
Units: Subjects			
Asian	3	3	6
Black or African American	0	2	2
White	31	27	58
Other	1	1	2
PANNS Total score			
Units: units on a scale			
arithmetic mean	102.3	101.6	
standard deviation	± 12	± 11.95	-
CGI-S score			
Units: units on a scale			
arithmetic mean	4.8	4.9	

standard deviation	± 0.57	± 0.55	-

End points

End points reporting groups

Reporting group title	PC Period - Risperidone
Reporting group description:	
Single (patient)-blinded treatment period with risperidone for 6 weeks	
Reporting group title	PC Period - Olanzapine
Reporting group description:	
Single (patient)-blinded treatment period with olanzapine for 6 weeks	
Reporting group title	DBT, Lu AF35700 10 mg
Reporting group description:	
Eligible patients from PC Period (based on criteria to which invetsigator and patient are blinded), will be randomly assigned (1:1) double-blind treatment in DBT Period, 8 weeks. Lu AF35700: 10 mg/day, encapsulated tablets, orally	
Reporting group title	DBT, Continued Treatment
Reporting group description:	
Eligible patients from PC Period (based on crietria to which investigator and patient are blinded), will be randomly assigned (1:1) double-blind treatment in DBT Period, 8 weeks. Patients in this arm will continue with the same treatment and dose as at last visit of PC Period. Risperidone: 4-6 mg/day, encapsulated tablets, orally. Olanzapine: 15-20 mg/day, encapsulated tablets, orally	

Primary: Change From Randomization to Week 8 in Positive and Negative Syndrome Scale (PANNS) Total Score

End point title	Change From Randomization to Week 8 in Positive and Negative Syndrome Scale (PANNS) Total Score
End point description:	
PANSS total score administered by the investigator. It included a total of 30 items that evaluated the Positive Symptoms subscale, the Negative Symptoms subscale, the General Psychopathology subscale. Each item is rated from 1 (symptom not present) to 7 (symptom extremely severe). PANSS total score was calculated as sum of all the items on the scale and ranged from 30 to 210. A negative score indicates an improvement compared to Randomization.	
End point type	Primary
End point timeframe:	
From Randomization to Week 8	

End point values	DBT, Lu AF35700 10 mg	DBT, Continued Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: units on a scale				
least squares mean (standard error)	-4.71 (± 2.22)	-10.19 (± 2.16)		

Statistical analyses

Statistical analysis title	Superiority Lu AF35700 10mg vs Continued Treatment

Statistical analysis description:

Only patients randomized to receive double blind treatment in the DBT Period are analyzed. Overall Number of Participants Analyzed in the FAS with a week 8 observation

Comparison groups	DBT, Lu AF35700 10 mg v DBT, Continued Treatment
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0809 [2]
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	5.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	11.65

Notes:

[1] - The mean changes from randomization in PANNS total score was analysed using a MMRM approach. The model included the fixed, categorical effects of treatment, country, week, treatment-by-week interaction, PC Period Treatment-by-week interaction, and the continuous covariates of Randomization score and Randomizaion-score-by-week interaction with an unstructured covariance structure to model the within-patient errors

[2] - Multiplicity adjustment was planned for the testing of the primary endpoint, but was not applied, since all p-values >0.05

Secondary: Change From Randomization to Week 8 in Global Clinical Impression – Severity of Illness (CGI-S) Score

End point title	Change From Randomization to Week 8 in Global Clinical Impression – Severity of Illness (CGI-S) Score

End point description:

CGI-S provides the clinician’s impression of the patient’s current state of mental illness. The clinician uses his or her clinical experience of this patient population to rate the severity of the patient's current mental illness on a 7-point scale ranging from 1 (normal - not at all ill) to 7 (among the most extremely ill patients). Higher scores indicate worsening

End point type	Secondary

End point timeframe:

From randomization to week 8

End point values	DBT, Lu AF35700 10 mg	DBT, Continued Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: units on a scale				
least squares mean (standard error)	-0.18 (± 0.12)	-0.37 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in 16-item Negative Symptom Assessment (NSA-16 Total) Score

End point title	Change From Randomization to Week 8 in 16-item Negative Symptom Assessment (NSA-16 Total) Score

End point description:

16 items arranged in 5 subdomains: communication dysfunction (items 1 to 4), emotional/affective dysfunction (items 5 to 7), dysfunction in sociality (items 8 to 10), motivational/hedonic dysfunction (items 11 to 14), and reduced psychomotor activity (items 15 and 16), and a Global Negative Symptom Rating. NSA-16 items are rated on a 6-point scale from 1 (behaviour is normal) to 6 (behaviour severely reduced), and a score of 9 if the item is not-rateable. The Global Negative Symptom Rating is rated from 1 (no evidence of symptoms) to 7 (extremely severe symptoms). The 16 items are summed to yield a total score ranging from 16 to 96 and the global rating ranges from 1 to 7.

End point type	Secondary

End point timeframe:

From randomization to Week 8

End point values	DBT, Lu AF35700 10 mg	DBT, Continued Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: units on a scale				
least squares mean (standard error)	-2.99 (± 1.64)	-3.14 (± 1.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Randomization to Week 8 in PANSS Negative Factor Score (Marder Negative Score)

End point title	Change From Randomization to Week 8 in PANSS Negative Factor Score (Marder Negative Score)

End point description:

The PANSS Negative Factor score is a subset of the PANSS assessing negative symptoms of schizophrenia. The factor consist of the seven items: blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, lack of spontaneity, motor retardation, and active social avoidance which are each rated on a 7-point scale, from 1=absent to 7=extreme. The PANSS Negative Factor score (7 items) range from 7 to 49 with a higher score indicating greater severity of symptoms.

End point type	Secondary

End point timeframe:

From Randomization to Week 8

End point values	DBT, Lu AF35700 10 mg	DBT, Continued Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: units on a scale				
least squares mean (standard error)	-1.51 (± 0.77)	-1.74 (± 0.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Response

End point title	Response

End point description:

End point type	Secondary

End point timeframe:

From randomization to Week 8

End point values	DBT, Lu AF35700 10 mg	DBT, Continued Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	31		
Units: participants	6	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 20 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Prospective Confirmation (PC) Period - Risperidone
Reporting group description: -	
Reporting group title	PC Period - Olanzapine
Reporting group description: -	
Reporting group title	Double Blind Treatment (DBT) Period - Lu AF35700 1
Reporting group description: -	
Reporting group title	DBT - Period Lu AF35700 20 mg
Reporting group description: -	

Serious adverse events	Prospective Confirmation (PC) Period - Risperidone	PC Period - Olanzapine	Double Blind Treatment (DBT) Period - Lu AF35700 1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 68 (1.47%)	1 / 51 (1.96%)	0 / 35 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 68 (0.00%)	1 / 51 (1.96%)	0 / 35 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 51 (0.00%)	0 / 35 (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

Serious adverse events	DBT - Period Lu AF35700 20 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Prospective Confirmation (PC) Period - Risperidone	PC Period - Olanzapine	Double Blind Treatment (DBT) Period - Lu AF35700 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 68 (25.00%)	3 / 51 (5.88%)	9 / 35 (25.71%)
Investigations			
Weight increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 51 (0.00%)	1 / 35 (2.86%)
occurrences (all)	1	0	1
Nervous system disorders			
Akathisia			
subjects affected / exposed	4 / 68 (5.88%)	0 / 51 (0.00%)	0 / 35 (0.00%)
occurrences (all)	4	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 68 (8.82%)	1 / 51 (1.96%)	4 / 35 (11.43%)
occurrences (all)	7	1	4
Insomnia			
subjects affected / exposed	4 / 68 (5.88%)	0 / 51 (0.00%)	1 / 35 (2.86%)
occurrences (all)	4	0	1
Schizophrenia			
subjects affected / exposed	1 / 68 (1.47%)	2 / 51 (3.92%)	2 / 35 (5.71%)
occurrences (all)	1	2	2

Non-serious adverse events	DBT - Period Lu AF35700 20 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 33 (24.24%)		
Investigations			
Weight increased			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	3		
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 33 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Schizophrenia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2018	PA2: This amendment has been prepared to revise the definition of patients with early-in-disease (ED) treatment-resistant schizophrenia (TRS) in protocol edition 2.0. The definition of ED TRS has been extended to include patients with schizophrenia first diagnosed <10 years prior to the Screening Visit, who will have failed at least 2 adequate treatment trials with an antipsychotic drug. The patient cohort in Study 17303A will now be continuous for all eligible patients, irrespective of the number of years prior to the Screening Visit when they were first diagnosed with schizophrenia. This more inclusive cohort will allow for more thorough analysis of the effects of Lu AF35700 in patients with ED TRS, without missing information from patients who are designated to have TRS but were diagnosed with schizophrenia between 5 to 10 years prior to the Screening Visit. The proposed analyses will include patients with ED TRS or LD TRS, as well as patients with TRS first diagnosed ≤5 years prior to the Screening Visit. In addition, this amendment has been prepared to make some clarifications and elaborations to protocol edition 2.0.
07 September 2018	PA3: This amendment has been prepared to increase the statistical power and geographic presence of the study to allow the use of the study data for confirmatory purposes. The number of patients to be randomized in the study has been increased and the targeted ratio of patients with early-in-disease (ED) treatment-resistant schizophrenia (TRS) to patients with late-in-disease (LD) TRS has been revised. The target ratio of patients with ED TRS versus LD TRS has been adjusted from 2:1 to 1:2. A ratio of 1:2 will more closely approximate the ratio of patients with ED versus LD TRS patients in the other ongoing phase III efficacy Study 16159A and 1:2 is also the ratio generally prevalent in the disease community. In addition, the change in target ratio is expected to facilitate recruitment. The objectives of the trial remain the same despite the change in sample size and ratio. The number of patients to be randomized in the study has been increased from 150 to 490. With the change in ratio of patients with ED TRS versus LD TRS (from 2:1 to 1:2) Study 17303A is aligned with Study 16159A and the assumptions regarding treatment effect size from Study 16159A has been applied to the sample size recalculation for Study 17303A. Further, the sample size recalculation was done to increase (from 80% to more than 90%) the power of the study. With this amendment to the protocol, the study may serve as a second confirmatory study in the development program for Lu AF35700 for a TRS indication. Study 17303A has from the beginning used the same study methodology as Study 16159A with similar inclusion and exclusion criteria. For its entire duration, Study 17303A has been conducted to the same high quality standard as Study 16159A and will continue to be so after the enlargement of the study.

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.

The study was terminated early and hence the statistical analysis was conducted on a smaller sample size than originally planned

Notes: