Clinical trial results:
Interventional, randomised, double-blind, active-controlled, fixed-dose study of Lu AF35700 in patients with Treatment-resistant Schizophrenia

Summary

EudraCT number	2014-003569-12
Trial protocol	ES EE FI CZ SK BG PL
Global end of trial date	08 October 2018

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	16159A Daybreak

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02717195
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, 45 36301311, lundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, 45 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	08 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2018
Global end of trial reached?	Yes
Global end of trial date	08 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of 10 and 20 mg/day of Lu AF35700 on schizophrenia symptoms in patients with 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	15 March 2016
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: 33
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Bulgaria: 140
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Estonia: 17
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Mexico: 106
Country: Number of subjects enrolled	Russian Federation: 190
Country: Number of subjects enrolled	Serbia: 72
Country: Number of subjects enrolled	Ukraine: 79
Country: Number of subjects enrolled	United States: 416
Worldwide total number of subjects	1098
EEA total number of subjects	230

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)	1073
From 65 to 84 years	25
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	Prospective Confirmation (PC) Period - Risperidone

Arm description: -

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: -

Arm type	Experimental
Investigational medicinal product name	Olanzapine
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	Prospective Confirmation (PC) Period - Risperidone	PC period - Olanzapine
Started	711	387
Completed	421	276
Not completed	290	111
Sponsor requested	-	1
Technical error	1	-

Change of place of residence	1	-
Apato Abulcasis syndrome	-	1
Subject took exclusionary medication	-	1
Did not fulfill rand criteria for DBT	189	75
Patient fraud with payment	1	-
Lack of results for blood levels	1	-
Low level of drug in the blood	1	-
Duplicate subject	1	-
Consent withdrawn by subject	43	12
Patient decision	5	2
Adverse event, non-fatal	19	7
non compliance with IMP	7	-
Investigator decision	2	1
Lost to follow-up	9	4
Positive Urine Drug Screen	-	1
Enrolled but not treated	3	3
Sub-therapeutic levels blood levels of Olanzapin	1	-
Non-compliance with IMP	-	1
Lack of efficacy	2	1
Protocol deviation	3	1
Non compliance with protocol	1	-

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 investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period, 10 weeks. Lu AF35700: 10 mg/day, encapsulated tablets, orally

Arm type	Experimental

Investigational medicinal product name	Lu AF35700 10 mg
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, Lu AF35700 20 mg

Arm description:

Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period, 10 weeks. Lu AF35700: 20 mg/day, encapsulated tablets, orally

Arm type	Experimental
Investigational medicinal product name	DBT, Lu AF35700 20 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Lu AF35700: 20 mg/day, encapsulated tablets, orally

Arm title	DBT, Continued treatment from PC period

Arm description:

Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period,10 weeks. Patients in this arm will continue with same the 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	Olanzapine
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: Patients are randomized at the start of Period 2, therefor period 2 can be seen as the baseline period, whereas period 1 is a lead-in period.

Number of subjects in period 2[2]	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period
Started	235	232	230
Completed	198	188	200
Not completed	37	44	30
Family circumstances	-	-	1

Change of place of residence	-	1	1
Patient missed required visits	-	1	1
Psychosocial issues	1	-	-
Needed antidepressant medication	-	-	1
Consent withdrawn by subject	14	13	8
Patient decision	-	2	2
Adverse event, non-fatal	10	11	8
Investigator decision	-	1	1
Lost to follow-up	-	3	2
Enrolled but not treated	1	-	-
Non-compliance with IMP	4	3	2
Lack of efficacy	6	9	2
Protocol deviation	1	-	1

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 investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period, 10 weeks. Lu AF35700: 10 mg/day, encapsulated tablets, orally

Reporting group title	DBT, Lu AF35700 20 mg

Reporting group description:

Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period, 10 weeks. Lu AF35700: 20 mg/day, encapsulated tablets, orally

Reporting group title	DBT, Continued treatment from PC period

Reporting group description:

Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period,10 weeks. Patients in this arm will continue with same the 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, Lu AF35700 20 mg	DBT, Continued treatment from PC period
Number of subjects	235	232	230
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	42.6	42.3	43.2
standard deviation	± 12.14	± 11.44	± 11.19
Gender categorical Units: Subjects			
Female	91	94	89
Male	144	138	141
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	36	33	34

White	176	179	178
More than one race	0	0	0
Unknown or Not Reported	22	19	17
PANNS total score			
Units: units on a scale			
arithmetic mean	96.96	98.23	98.40
standard deviation	± 9.17	± 9.29	± 9.84

Reporting group values	Total		
Number of subjects	697		
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			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	274		
Male	423		
Race			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	103		
White	533		
More than one race	0		
Unknown or Not Reported	58		
PANNS total score			
Units: units on a scale			
arithmetic mean			
standard deviation	-		

End points

End points 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	DBT, Lu AF35700 10 mg
Reporting group description:	
Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period, 10 weeks. Lu AF35700: 10 mg/day, encapsulated tablets, orally	
Reporting group title	DBT, Lu AF35700 20 mg
Reporting group description:	
Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period, 10 weeks. Lu AF35700: 20 mg/day, encapsulated tablets, orally	
Reporting group title	DBT, Continued treatment from PC period
Reporting group description:	
Eligible patients from PC Period (based on criteria to which investigator and patient are blinded), will be randomly assigned (1:1:1) double-blind treatment in DBT Period,10 weeks. Patients in this arm will continue with same the 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 10 in Positive and Negative Syndrome Scale (PANSS) Total Score

End point title	Change From Randomization to Week 10 in Positive and Negative Syndrome Scale (PANSS) Total Score
End point description:	
Positive and Negative Syndrome Scale (PANSS) total score administered by the investigator. It included 3 sub-scales with 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 higher score corresponded to a worse severity of schizophrenia.	
End point type	Primary
End point timeframe:	
From Randomization to Week 10	

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	189	202	
Units: units on a scale				
least squares mean (standard error)	-10.01 (± 0.96)	-8.22 (± 0.98)	-9.90 (± 0.97)	

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 is number of patients in the FAS with a week 10 observation.

Comparison groups	DBT, Lu AF35700 10 mg v DBT, Continued treatment from PC period
Number of subjects included in analysis	403
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.9196 [2]
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.37
upper limit	2.13

Notes:

[1] - The mean changes from Randomization in PANSS 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, PC Period treatment-by-week interaction, and the continuous covariates of Randomization score and Randomization 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

Statistical analysis title	Superiority Lu AF35700 20mg vs Continued Treatment

Statistical analysis description:

Only patients randomized to receive double-blind treatment in the DBT Period are analysed. Overall Number of Participants Analysed is number of patients in the FAS with a week 10 observation.

Comparison groups	DBT, Lu AF35700 20 mg v DBT, Continued treatment from PC period
Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1474 [4]
Method	Mixed Models Repeared Measures
Parameter estimate	Mean difference (final values)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	3.94

Notes:

[3] - The mean changes from Randomization in PANSS total score was analyzed using a MMRM approach. The model included the fixed, categorical effects of treatment, country, week, treatment-by-week interaction, PC Period treatment, PC Period treatment-by-week interaction, and the continuous covariates of Randomization score and Randomization score-by-week interaction with an unstructured covariance structure to model the within-patient errors.
[4] - 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 10 in PSP Total Personal and

Social Performance (PSP) Total Score

End point title	Change From Randomization to Week 10 in PSP Total Personal and Social Performance (PSP) Total Score

End point description:

PSP is a clinician-rated scale designed and validated to measure a patient's current level of social functioning. It consists of 4 items: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviours. Each items were assessed on a 6-point scale, from 1 (absent) to 6 (very severe). PSP score was calculated as sum of all the items on the scale and ranged from 4 to 100. A higher score represents more severe functional impairment.

End point type	Secondary

End point timeframe:

From Randomization to Week 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	204	197	203	
Units: units on a scale				
least squares mean (standard error)	4.90 (± 0.96)	3.23 (± 0.98)	3.94 (± 0.98)	

Statistical analyses

Statistical analysis title	Lu AF35700 10 mg vs Continued Treatment
Comparison groups	DBT, Lu AF35700 10 mg v DBT, Continued treatment from PC period
Number of subjects included in analysis	407
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.2998 [6]
Method	Mixed Models Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.86
upper limit	2.78

Notes:

[5] - The mean changes from Randomization in PSP 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, PC Period treatment-by-week interaction, and the continuous covariates of Randomization score and Randomization score-by-week interaction with an unstructured covariance structure to model the within-patient errors.

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

Statistical analysis title	Lu AF35700 20 mg vs Continued Treatment

Statistical analysis description:

The mean changes in PSP score was analysed using an MMRM approach. The model included the fixed, categorical effects of treatment , country, week, treatment-by-week interaction, PC Period treatment ,

PC Period treatment-by-week interaction, and the continuous covariates of Randomization score and Randomization score-by-week interaction with an unstructured covariance structure to model the within-patient errors.

Comparison groups	DBT, Lu AF35700 20 mg v DBT, Continued treatment from PC period
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4478 [7]
Method	Mixed Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.54
upper limit	1.12

Notes:

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

Secondary: Change From Randomization to Week 10 in Global Clinical Impression - Severity of Illness (CGI-S) Score

End point title	Change From Randomization to Week 10 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 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	232	231	228	
Units: units on a scale				
least squares mean (standard error)	-0.59 (± 0.06)	-0.54 (± 0.06)	-0.57 (± 0.06)	

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 10, Defined as ≥20% Reduction in PANSS Total Score, PANSS (Positive and Negative Syndrome Scale) Total Score ≤70, CGI-S (Clinical Global Impression Scale - Severity of Illness) Score <4

End point title	Response at Week 10, Defined as ≥20% Reduction in PANSS

	Total Score, PANSS (Positive and Negative Syndrome Scale) Total Score ≤70, CGI-S (Clinical Global Impression Scale - Severity of Illness) Score <4

End point description:

PANSS total score administered by the investigator. It included 3 sub-scales with 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 higher score corresponded to a worse severity of schizophrenia. A reduction in score indicates improvement.
The Clinical Global Impression scale - severity of illness (CGI-S) is administered by the investigator. The patient is rated on a 7-point scale ranging from 1 (Normal - not at all ill) to 7 (among the most extremely ill patients). A reduction in scale indicates improvement.

End point type	Secondary

End point timeframe:

From Randomization to Week 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	189	202	
Units: participants	21	18	12	

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 10, Defined as ≥20% Reduction in Positive and Negative Syndrome Scale (PANSS) Total Score From Randomization

End point title	Response at Week 10, Defined as ≥20% Reduction in Positive and Negative Syndrome Scale (PANSS) Total Score From Randomization

End point description:

PANSS total score administered by the investigator. It included 3 sub-scales with 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 higher score corresponded to a worse severity of schizophrenia. A reduction in score indicates improvement.

End point type	Secondary

End point timeframe:

From Randomization to Week 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	189	202	
Units: participants	82	59	77	

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 10, Defined as ≥30% Reduction in PANSS Total Score From Randomization

End point title	Response at Week 10, Defined as ≥30% Reduction in PANSS Total Score From Randomization

End point description:

Positive and Negative Syndrome Scale (PANSS) total score administered by the investigator. It included 3 sub-scales with 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 higher score corresponded to a worse severity of schizophrenia. A reduction in score indicates improvement.

End point type	Secondary

End point timeframe:

From Randomization to Week 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	189	202	
Units: participants	42	30	45	

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 10, Defined as ≥40% Reduction in Positive and Negative Syndrome Scale (PANSS) Total Score From Randomization

End point title	Response at Week 10, Defined as ≥40% Reduction in Positive and Negative Syndrome Scale (PANSS) Total Score From Randomization

End point description:

PANSS total score administered by the investigator. It included 3 sub-scales with 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 higher score corresponded to a worse severity of schizophrenia. A reduction in score indicates improvement.

End point type	Secondary

End point timeframe:

From Randomization to Week 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	189	202	
Units: participants	23	15	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 10, Defined as ≥50% Reduction in Positive and Negative Syndrome Scale (PANSS) Total Score From Randomization

End point title	Response at Week 10, Defined as ≥50% Reduction in Positive and Negative Syndrome Scale (PANSS) Total Score From Randomization

End point description:

PANSS total score administered by the investigator. It included 3 sub-scales with 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 higher score corresponded to a worse severity of schizophrenia. A reduction in score indicates improvement.

End point type	Secondary

End point timeframe:

From Randomization to Week 10

End point values	DBT, Lu AF35700 10 mg	DBT, Lu AF35700 20 mg	DBT, Continued treatment from PC period	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	201	189	202	
Units: participants	10	4	6	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
22 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	DBT Lu AF35700, 10 mg
Reporting group description: -	
Reporting group title	DBT Lu AF35700, 20 mg
Reporting group description: -	
Reporting group title	DBT period, continued treatment from PC period
Reporting group description: -	

Serious adverse events	Prospective Confirmation (PC) Period - Risperidone	PC period - Olanzapine	DBT Lu AF35700, 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 708 (1.98%)	7 / 384 (1.82%)	6 / 234 (2.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intentional overdose			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive emergency			

subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	1 / 234 (0.43%)
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			
Myocardial infarction			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	1 / 234 (0.43%)
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			
Psychosocial support			
subjects affected / exposed	1 / 708 (0.14%)	0 / 384 (0.00%)	0 / 234 (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
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 708 (0.00%)	1 / 384 (0.26%)	0 / 234 (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
General disorders and administration site conditions			
Vascular stent thrombosis			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Social stay hospitalisation			

subjects affected / exposed	1 / 708 (0.14%)	1 / 384 (0.26%)	0 / 234 (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
Gastrointestinal disorders			
Intestinal haemorrhage			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 708 (0.14%)	0 / 384 (0.00%)	0 / 234 (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
Pulmonary thrombosis			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 708 (0.14%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranoia			
subjects affected / exposed	2 / 708 (0.28%)	1 / 384 (0.26%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Psychotic disorder			
subjects affected / exposed	1 / 708 (0.14%)	1 / 384 (0.26%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	5 / 708 (0.71%)	1 / 384 (0.26%)	1 / 234 (0.43%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	2 / 708 (0.28%)	1 / 384 (0.26%)	2 / 234 (0.85%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 708 (0.00%)	0 / 384 (0.00%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 708 (0.00%)	1 / 384 (0.26%)	0 / 234 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DBT Lu AF35700, 20 mg	DBT period, continued treatment from PC period	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 232 (2.16%)	5 / 230 (2.17%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	1 / 232 (0.43%)	0 / 230 (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			
Intentional overdose			

subjects affected / exposed	0 / 232 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive emergency			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Psychosocial support			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Multiple sclerosis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Vascular stent thrombosis			

subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal haemorrhage			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 232 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 232 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			

subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	1 / 232 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	2 / 232 (0.86%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 232 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 232 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 232 (0.00%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Prospective Confirmation (PC) Period - Risperidone	PC period - Olanzapine	DBT Lu AF35700, 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 708 (8.47%)	45 / 384 (11.72%)	20 / 234 (8.55%)
Investigations			
Weight increased			
subjects affected / exposed	5 / 708 (0.71%)	1 / 384 (0.26%)	8 / 234 (3.42%)
occurrences (all)	5	1	8
Nervous system disorders			
Akathisia			
subjects affected / exposed	36 / 708 (5.08%)	8 / 384 (2.08%)	3 / 234 (1.28%)
occurrences (all)	37	8	4
Headache			
subjects affected / exposed	24 / 708 (3.39%)	16 / 384 (4.17%)	11 / 234 (4.70%)
occurrences (all)	25	18	12
Somnolence			
subjects affected / exposed	34 / 708 (4.80%)	30 / 384 (7.81%)	3 / 234 (1.28%)
occurrences (all)	35	31	3

Non-serious adverse events	DBT Lu AF35700, 20 mg	DBT period, continued treatment from PC period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 232 (17.24%)	25 / 230 (10.87%)	
Investigations			
Weight increased			
subjects affected / exposed	19 / 232 (8.19%)	11 / 230 (4.78%)	
occurrences (all)	19	11	
Nervous system disorders			
Akathisia			
subjects affected / exposed	5 / 232 (2.16%)	4 / 230 (1.74%)	
occurrences (all)	5	4	
Headache			
subjects affected / exposed	15 / 232 (6.47%)	10 / 230 (4.35%)	
occurrences (all)	16	11	
Somnolence			
subjects affected / exposed	9 / 232 (3.88%)	4 / 230 (1.74%)	
occurrences (all)	9	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2016	PA1: A urine dipstick pregnancy test at Baseline was added. Definition of a completer was changed to: "a subject who has completed the treatment period including any following follow up activities is considered to have completed the study". Ethics: text was changed to ensure that only patients who were able to consent for themselves were included in the study. Treatment regimen: wording was clarified on how switch should occur to avoid accidental overdosing. Post-study access to IMP(s): information regarding extension Study 16159B was added. Safety follow-up Visit (Visit 13): error corrected; it was specified that AEs ongoing after the end of the treatment period will be followed up at the Safety Follow-up Visit, and that no new non SAEs will be captured after the end of the treatment period. Error corrected; B basophils added to Panel 3. Genotyping: update in according with the analysis kit used by Covance Department of Genomics. Additional alleles added for test.
30 September 2016	PA2: Study population: the period for treatment with an adequate (previously same) antipsychotic dose prior to screening has been reduced from 6 weeks to 2 weeks. Exclusion Criterion 13: guidance added for evaluation of treatment improvement in the last 2 years prior to Screening. CYP1A2 inhibitors were added as concomitant medication not permitted during the study.
04 October 2016	PA3: It was added that the analysis of PK assessments in the DBT Period will also include Lu AF36152, risperidone, 9 OH risperidone, and olanzapine. Exclusion criterion 25: the criterion defining unstable co-morbid diabetes were changed to reflect the disease in a patient with schizophrenia. Exclusion criterion 26 was deleted; patients with schizophrenia who meet the laboratory test criteria for co-morbid diabetes will not be excluded from participating in the study. Treatment regimen: time of dosing at each visit, including changing in dosing times, was more clearly defined. Assessments: complete description of questionnaires used for assessment of the PANSS (PANSS informant data is specified). It was specified that prolactin test results 250 g / L must be followed up. Limiting of re-sampling. Statistical Methodology: analysis of subgroups was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported