Clinical trial results:
Interventional, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Fixed-Flexible-Dose Study of Lu AF11167 for the Treatment of Persistent Prominent Negative Symptoms in Patients With Schizophrenia

Summary

EudraCT number	2018-001581-42
Trial protocol	EE LV HU BG PL CZ
Global end of trial date	03 September 2020

Results information

Result version number	v1 (current)
This version publication date	03 September 2021
First version publication date	03 September 2021

Trial information

Trial identification

Sponsor protocol code	17972A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03793712
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Otilliavej 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	03 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2020
Global end of trial reached?	Yes
Global end of trial date	03 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the efficacy of 2 fixed-flexible doses (1-2 milligrams [mg]/day and 3-4 mg/day) of Lu AF11167 as monotherapy on negative symptoms in participants with schizophrenia with persistent prominent negative symptoms.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 December 2018
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	Bulgaria: 68
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Ukraine: 60
Worldwide total number of subjects	162
EEA total number of subjects	102

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)	162
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study design included a 1- to 4-week Screening and Washout Period (to assess the eligibility of participants), a 1-week Placebo Run-in Period (to confirm the stability of participant's clinical condition as well as persistence of their prominent negative symptoms), a 12-week Double-blind Treatment Period, and a 2-week Safety Follow-up Period.

Pre-assignment

Screening details:

Participants were randomly assigned (1:1:1) to double-blind treatment with Lu AF11167 1-2 mg/day, Lu AF11167 3-4 mg/day, or placebo for 12 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo matched to Lu AF11167 tablet orally once daily for a total of 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to Lu AF11167 will be administered per schedule specified in the arm description.

Arm title	Lu AF11167 1-2 mg/day

Arm description:

Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. If this dose was not tolerated after the first week of treatment, the dose was reduced to 1 mg/day once daily and participants stayed on that dose for the remainder of the study. Total treatment duration was 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Lu AF11167
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Lu AF11167 will be administered per dose and schedule specified in the arm description.

Arm title	Lu AF11167 3-4 mg/day

Arm description:

Participants received Lu AF11167 tablet orally once daily at a starting dose of 4 mg/day. If this dose was not tolerated after the first week of treatment, the dose was reduced to 3 mg/day once daily and participants stayed on that dose for the remainder of the study. Total treatment duration was 12 weeks.

Arm type	Experimental

Investigational medicinal product name	Lu AF11167
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Modified-release tablet
Routes of administration	Oral use

Dosage and administration details:

Lu AF11167 will be administered per dose and schedule specified in the arm description.

Number of subjects in period 1	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day
Started	54	54	54
Received at Least 1 Dose of Study Drug	54	54	54
Completed	39	36	36
Not completed	15	18	18
Consent withdrawn by subject	4	1	5
Adverse event, non-fatal	2	5	4
Other than specified	7	12	8
Lack of efficacy	2	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to Lu AF11167 tablet orally once daily for a total of 12 weeks.	
Reporting group title	Lu AF11167 1-2 mg/day
Reporting group description:	
Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. If this dose was not tolerated after the first week of treatment, the dose was reduced to 1 mg/day once daily and participants stayed on that dose for the remainder of the study. Total treatment duration was 12 weeks.	
Reporting group title	Lu AF11167 3-4 mg/day
Reporting group description:	
Participants received Lu AF11167 tablet orally once daily at a starting dose of 4 mg/day. If this dose was not tolerated after the first week of treatment, the dose was reduced to 3 mg/day once daily and participants stayed on that dose for the remainder of the study. Total treatment duration was 12 weeks.	

Reporting group values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day
Number of subjects	54	54	54
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 41.65 ± 9.227	 43.2 ± 8.888	 43.04 ± 9.546
Gender Categorical Units: Subjects			
Female	20	22	23
Male	34	32	31

Reporting group values	Total		
Number of subjects	162		
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender Categorical Units: Subjects			
Female	65		
Male	97		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo matched to Lu AF11167 tablet orally once daily for a total of 12 weeks.	
Reporting group title	Lu AF11167 1-2 mg/day
Reporting group description:	
Participants received Lu AF11167 tablet orally once daily at a starting dose of 2 mg/day. If this dose was not tolerated after the first week of treatment, the dose was reduced to 1 mg/day once daily and participants stayed on that dose for the remainder of the study. Total treatment duration was 12 weeks.	
Reporting group title	Lu AF11167 3-4 mg/day
Reporting group description:	
Participants received Lu AF11167 tablet orally once daily at a starting dose of 4 mg/day. If this dose was not tolerated after the first week of treatment, the dose was reduced to 3 mg/day once daily and participants stayed on that dose for the remainder of the study. Total treatment duration was 12 weeks.	

Primary: Change From Baseline in Brief Negative Symptom Scale (BNSS) Total Score at Week 12

End point title	Change From Baseline in Brief Negative Symptom Scale (BNSS) Total Score at Week 12
End point description:	
The BNSS is a brief clinician rating scale, intended to measure negative symptoms. It consists of 13 items organized into 6 subscales: anhedonia, distress, asociality, avolition, blunted affect and alogia. The items score the impairment. Items 1 to 4 were rated from 0 (Normal) to 6 (Extremely severe) and items 5 to 13 were rated from 0 (No impairment) to 6 (Severe deficit). The BNSS total score was calculated by summing the 13 individual items. The BNSS total scores range from 0 to 78. Full analysis set (FAS) included all randomized participants who took at least 1 dose of the double-blind study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed' = participants analyzed for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
least squares mean (standard error)	-6.83 (± 0.97)	-5.70 (± 0.99)	-5.96 (± 0.98)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Analysis was performed using a restricted maximum likelihood-based mixed model for repeated measurements (MMRM) approach. The model included pooled country, visit, and treatment as fixed factors, and the Baseline BNSS total score as a continuous covariate. The treatment-by-week interaction	

and the Baseline BNSS total score-by-week interaction were also included.

Comparison groups	Placebo v Lu AF11167 1-2 mg/day
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4076
Method	Mixed models analysis
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.56
upper limit	3.82
Variability estimate	Standard error of the mean
Dispersion value	1.36

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using a restricted maximum likelihood-based MMRM approach. The model included pooled country, visit, and treatment as fixed factors, and the Baseline BNSS total score as a continuous covariate. The treatment-by-week interaction and the Baseline BNSS total score-by-week interaction were also included.

Comparison groups	Placebo v Lu AF11167 3-4 mg/day
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5197
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	3.55
Variability estimate	Standard error of the mean
Dispersion value	1.36

Secondary: Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Marder Negative Symptom Factor score: Negative Symptoms at Week 12

End point title	Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Marder Negative Symptom Factor score: Negative Symptoms at Week 12

End point description:

PANSS is a clinician rated scale designed to measure severity of psychopathology in adult participants with schizophrenia, schizoaffective disorders and other psychotic disorders. It includes 3 sub-scales and 30 items: 7 items for positive scale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items for negative scale (for example: blunted affect, emotional withdrawal,

and poor rapport) and 16 items for general psychopathology scale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (no symptoms) to 7 (extremely severe symptom). PANSS total score: sum of all items and ranges from 30 to 210. Subscale scores: sum of items within each subscale. FAS: all randomized participants who took at least 1 dose of double-blind study drug and who had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed'=participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
least squares mean (standard error)	-4.19 (± 0.54)	-3.55 (± 0.55)	-3.16 (± 0.54)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PANSS Negative Subscale Score at Week 12

End point title	Change From Baseline in PANSS Negative Subscale Score at Week 12

End point description:

PANSS is a clinician rated scale designed to measure severity of psychopathology in adult participants with schizophrenia, schizoaffective disorders, and other psychotic disorders. It includes 3 sub-scales and 30 items: 7 items for positive scale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items for negative scale (for example: blunted affect, emotional withdrawal, and poor rapport) and 16 items for general psychopathology scale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (no symptoms) to 7 (extremely severe symptom). Subscale scores: sum of items within each subscale. FAS: all randomized participants who took at least 1 dose of double-blind study drug and who had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed'=participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	-3.82 (± 0.56)	-3.69 (± 0.58)	-3.13 (± 0.55)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression — Schizophrenia Severity of Illness (CGI-SCH-S) Negative Symptoms Score at Week 12

End point title	Change From Baseline in Clinical Global Impression — Schizophrenia Severity of Illness (CGI-SCH-S) Negative Symptoms Score at Week 12

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. The CGI-SCH severity of illness category symptoms and overall severity were rated on a 7-point scale ranging from 1 (normal - not ill) to 7 (among the most severely ill). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. FAS: all randomized participants who took at least 1 dose of the double-blind study drug and who had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
least squares mean (standard error)	-0.49 (± 0.09)	-0.47 (± 0.09)	-0.40 (± 0.09)	

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression — Schizophrenia Degree of Change (CGI-SCH-DC) Negative Symptoms Score at Week 12

End point title	Clinical Global Impression — Schizophrenia Degree of Change (CGI-SCH-DC) Negative Symptoms Score at Week 12

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. In the CGI-SCH degree of change category symptoms and overall severity were rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. FAS included all randomized participants who took at least 1 dose of the double-blind study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	3.56 (± 0.12)	3.44 (± 0.12)	3.54 (± 0.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With a CGI-SCH-DC Negative Symptoms Response at Week 12

End point title	Number of Participants With a CGI-SCH-DC Negative Symptoms Response at Week 12

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. In the CGI-SCH-DC degree of change category symptoms and overall severity were rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. CGI-SCH-DC negative symptoms response defined as a CGI-SCH-DC negative symptoms score of 1 or 2. All-patients-treated set (APTS) included all randomized participants who took at least 1 dose of the double-blind study drug. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: participants	1	3	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With BNSS Response at Week 12

End point title	Number of Participants With BNSS Response at Week 12

End point description:

The BNSS is a brief clinician rating scale, intended to measure negative symptoms. It consists of 13

items organized into 6 subscales: anhedonia, distress, asociality, avolition, blunted affect and alogia. The items score the impairment. Items 1 to 4 were rated from 0 (Normal) to 6 (Extremely severe) and items 5 to 13 were rated from 0 (No impairment) to 6 (Severe deficit). The BNSS total score was calculated by summing the 13 individual items. The BNSS total scores range from 0 to 78. BNSS response defined as a 20%, 30%, or 40% decrease in BNSS total score. APTS included all randomized participants who took at least 1 dose of the double-blind study drug. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: participants				
Decreased by at least 20%	15	9	14	
Decreased by at least 30%	5	4	4	
Decreased by at least 40%	1	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Personal and Social Performance Scale (PSP) Total Score at Week 12

End point title	Change From Baseline in Personal and Social Performance Scale (PSP) Total Score at Week 12

End point description:

The PSP is a clinician-rated scale designed and validated to measure a participant’s current level of social functioning. The PSP consists of 4 items: socially useful activities (including work and study), personal and social relationships, self-care, and disturbing and aggressive behaviours. The 4 items were assessed on a 6-point scale, from absent to very severe. Based on these assessments and their combination, individual scores were converted into a global score ranging from 1 to 100. FAS included all randomized participants who took at least 1 dose of the double-blind study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	7.28 (± 1.53)	7.39 (± 1.63)	5.61 (± 1.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PANSS Total Score at Week 12

End point title	Change From Baseline in PANSS Total Score at Week 12

End point description:

PANSS is a clinician rated scale designed to measure severity of psychopathology in adult participants with schizophrenia, schizoaffective disorders and other psychotic disorders. It includes 3 sub-scales and 30 items: 7 items for positive scale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items for negative scale (for example: blunted affect, emotional withdrawal, and poor rapport) and 16 items for general psychopathology scale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (no symptoms) to 7 (extremely severe symptom). PANSS total score: sum of all items and ranges from 30 to 210. Subscale scores: sum of items within each subscale. FAS: all randomized participants who took at least 1 dose of double-blind study drug and who had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed'=participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	-7.79 (± 1.09)	-7.42 (± 0.98)	-5.61 (± 1.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in PANSS Positive Subscale Scores at Week 12

End point title	Change From Baseline in PANSS Positive Subscale Scores at Week 12

End point description:

PANSS is a clinician rated scale designed to measure severity of psychopathology in adult participants with schizophrenia, schizoaffective disorders, and other psychotic disorders. It includes 3 sub-scales and 30 items: 7 items for positive scale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items for negative scale (for example: blunted affect, emotional withdrawal, and poor rapport) and 16 items for general psychopathology scale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (no symptoms) to 7 (extremely severe symptom). Subscale scores: sum of items within each subscale. FAS: all randomized participants who took at least 1 dose of double-blind study drug and who had a valid baseline and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed'=participants

analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	-0.67 (± 0.29)	-0.44 (± 0.22)	-0.29 (± 0.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CGI-SCH-S Overall Severity Score at Week 12

End point title	Change From Baseline in CGI-SCH-S Overall Severity Score at Week 12

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. The CGI-SCH severity of illness category symptoms and overall severity were rated on a 7-point scale ranging from 1 (normal - not ill) to 7 (among the most severely ill). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently, and no total score was derived. APTS included all randomized participants who took at least 1 dose of the double-blind study drug. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	-0.38 (± 0.12)	-0.11 (± 0.12)	-0.29 (± 0.08)	

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-SCH-DC Overall Severity Score at Week 12

End point title	CGI-SCH-DC Overall Severity Score at Week 12

End point description:

The CGI-SCH is a clinician-rated scale to assess global illness severity and degree of change in participants with schizophrenia. For both the global illness severity and degree of change, the CGI-SCH consists of 4 different groups of symptoms (positive, negative, cognitive, and depressive) and the overall severity of the disorder. In the CGI-SCH degree of change category symptoms and overall severity were rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Each single rating (conditions of severity and degree of improvement) and overall ratings of severity and improvement were scored independently and no total score was derived. CGI-SCH-DC negative symptoms response defined as a CGI-SCH-DC negative symptoms score of 1 or 2. APTS included all randomized participants who took at least 1 dose of the double-blind study drug. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	3.69 (± 0.11)	3.47 (± 0.10)	3.61 (± 0.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Total Score at Week 12

End point title	Change From Baseline in Calgary Depression Scale for Schizophrenia (CDSS) Total Score at Week 12

End point description:

The CDSS is a 9-item clinician rated scale specifically developed for the assessment of depression in participants with schizophrenia. The items on the CDSS were all typical depressive symptoms and do not appear to overlap with the negative symptoms of schizophrenia. All items were rated on a 4-point scale from 0 (absent) to 3 (severe). Anchor point descriptions were provided to aid differentiation between each item score. The first 8 items were rated on the basis of the participant’s responses to questions during a semi-structured interview; the ninth item was based on the clinician's assessment of the participant over the course of the interview. The total score ranges from 0 to 27. FAS included all randomized participants who took at least 1 dose of the double-blind study drug and who had a valid baseline assessment and at least 1 valid post-baseline assessment of the primary efficacy variable. 'Overall number of participants analyzed' = participants analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	Lu AF11167 1-2 mg/day	Lu AF11167 3-4 mg/day	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	36	38	
Units: units on a scale				
arithmetic mean (standard error)	-0.46 (± 0.18)	-0.25 (± 0.18)	-0.34 (± 0.17)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to Week 14	
Adverse event reporting additional description: APTS included all randomized participants who took at least 1 dose of the double-blind study drug.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	AF11167 1-2 mg
Reporting group description: AF11167 1-2 mg	
Reporting group title	AF11167 3-4 mg
Reporting group description: AF11167 3-4 mg	

Serious adverse events	Placebo	AF11167 1-2 mg	AF11167 3-4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)	0 / 54 (0.00%)	1 / 54 (1.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 54 (0.00%)	0 / 54 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	AF11167 1-2 mg	AF11167 3-4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 54 (16.67%)	16 / 54 (29.63%)	19 / 54 (35.19%)
Investigations			

Weight decreased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	3 / 54 (5.56%)
occurrences (all)	0	1	3
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	3 / 54 (5.56%)
occurrences (all)	0	1	3
Dizziness			
subjects affected / exposed	2 / 54 (3.70%)	0 / 54 (0.00%)	3 / 54 (5.56%)
occurrences (all)	2	0	3
Headache			
subjects affected / exposed	4 / 54 (7.41%)	3 / 54 (5.56%)	6 / 54 (11.11%)
occurrences (all)	4	3	8
Somnolence			
subjects affected / exposed	0 / 54 (0.00%)	4 / 54 (7.41%)	4 / 54 (7.41%)
occurrences (all)	0	4	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 54 (0.00%)	1 / 54 (1.85%)	5 / 54 (9.26%)
occurrences (all)	0	1	6
Insomnia			
subjects affected / exposed	2 / 54 (3.70%)	4 / 54 (7.41%)	1 / 54 (1.85%)
occurrences (all)	2	4	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 54 (3.70%)	4 / 54 (7.41%)	2 / 54 (3.70%)
occurrences (all)	2	4	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2018	This amendment was prepared to update the heart-rate corrected QT interval using Fridericia's correction formula (QTcF) withdrawal criteria, to update the Cogstate Schizophrenia Cognitive Battery, and to provide clarifications and corrections to the protocol.
13 December 2019	This amendment has been prepared to update inclusion criteria and exclusion criteria. Other minor clarifications and corrections were also made. - Inclusion criterion was changed for the participants being known and treated by the site or investigator from 12 months to 6 months to align eligibility requirements across other inclusion and exclusion criteria addressing stability of the participant. - Inclusion criterion was updated to allow a 2nd antipsychotic used for sleep problems, if approved by the Medical Monitor, as sleep problems are common in this participant population. - Inclusion criterion was updated to clarify that hospitalization for social reasons is not exclusionary. - Exclusion criterion was updated to allow thyroid stimulating hormone (TSH) values outside of the reference range if deemed not clinically significant by the investigator and approved by the Medical Monitor.
11 May 2020	This amendment has been prepared to increase the number of sites, add an interim analysis for futility, add that re-screening may be allowed in certain circumstances, and to add the United States as a participating country.

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.

Due to lack of efficacy based on the interim analysis, this study was terminated early.

Notes: