Clinical Study Protocol

Interventional, open-label, flexible-dose, long-term safety study of Lu AF35700 in adult patients with schizophrenia

Lu AF35700

Study No.:	16159B
EudraCT/IND No.:	2015-003284-11 (EU) / 116,335 (US)
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
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Synopsis – Study 16159B

Sponsor	**Investigational Medicinal Product**	**EudraCT/IND No.**
H. Lundbeck A/S	Lu AF35700	2015-003284-11 / 116,335

Title of Study

Interventional, open-label, flexible-dose long-term safety study of Lu AF35700 in adult patients with schizophrenia

Study Site(s) and Number of Patients Planned

120 sites are planned in approximately 15 countries (in-/out-patient clinics). The selected sites will be preferably the sites which participated in the study 16159A or in the study 16323A.

Approximately 400 patients with schizophrenia are planned to be enrolled with the following assumptions: 270 patients who will have completed the study 16159A, 30 patients who will have completed the dosing period of the study 16323A and 100 additional patients with schizophrenia for whom a switch of antipsychotic treatment can be potentially beneficial. The distribution of the number of patients may be adjusted based upon the recruitment rate in each group.

Objectives

- Primary objective:
  - to evaluate the safety and tolerability of the long-term treatment with Lu AF35700.
- Exploratory objectives:
  - to evaluate the long-term safety and tolerability of daily and weekly doses of Lu AF35700 in patients with schizophrenia during the 52-week treatment period
  - to evaluate the therapeutic effectiveness of daily and weekly doses of Lu AF35700 in patients with schizophrenia over a period of 52 weeks on:
    - psychotic symptoms
    - negative symptoms
    - global clinical impression
    - remission rate
    - quality of life and functioning
    - treatment satisfaction
    - health care resource utilisation

Study Methodology

- This study is a multi-national, multi-site, open-label, flexible-dose, long-term (52-week) safety study in patients with schizophrenia who have participated and completed a study investigating Lu AF35700 including studies 16159A and 16323A, or in patients with schizophrenia for whom a switch of antipsychotic treatment can be potentially beneficial according to the investigator's clinical judgement (either due to sub-optimal symptom control or lack of tolerability of their current antipsychotic treatment).
- The recruitment of patients who need to change their antipsychotic treatment can start in a given site only after the recruitment of the patients in the study 16159A or in the study 16323A is completed.
- The adjustment of Lu AF35700 dosing regimen (10 mg/day or 20 mg/day) during the course of the study will be left to the investigator's clinical judgement.
- For patients who have completed the study 16159A, the daily dosing regimen (10 mg/day or 20 mg/day) can be switched to weekly dosing regimen (70 mg/week) according to the investigator's clinical judgement. The number of patients under weekly dosing regimen will be limited to 50 patients by IVRS/IWRS.

For patients who completed study 16159A (16159A-patients)

- The Baseline Visit of this long-term safety study (study 16159B) will take place at the same visit as the Visit 12 (Primary Outcome Visit, end of Week 16) of the study 16159A.
- After the baseline assessment, for eligible patients, the treatment with Lu AF35700 will be initiated at daily

dose of 10 mg at Day 1 of study 16159B. In addition, for *16159A-patients*, the treatment (Lu AF35700, risperidone or olanzapine) received during study 16159A will be tapered down in a blinded fashion and will be completed in 7 days.

- At the end of the first week (Week 1 Visit), all patients will be treated with 10 mg/day Lu AF35700 only.
- From the Week 1 Visit, according to the investigator's clinical judgement, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment. This can occur at scheduled or unscheduled visits.
- From the Week 8 Visit, the switch from Lu AF35700 daily dosing regimen to Lu AF35700 weekly dosing regimen can be performed at any consecutive visit according to the investigator's clinical judgment. The first weekly tablet will be taken 7 days after the last daily tablet. The Lu AF35700 weekly dosing regimen can be switched back to a daily dosing regimen of 10 mg/day for tolerability reasons or to 20 mg/day for worsening of the patient's clinical status. This can occur at scheduled or unscheduled visits. The first daily tablet will be taken 7 days after the last weekly tablet.

For patients who completed the dosing period of the study 16323A (16323A-patients)

- The Baseline Visit of study 16159B will take place at the same visit as the last day of the dosing period of study 16323A.
- After the baseline assessment, for eligible patients, the treatment with Lu AF35700 will be initiated at daily dose of 10 mg at Day 1 of study 16159B. In addition, for *16323A-patients*, the treatment (Lu AF35700 or quetiapine) received during study 16323A will be tapered down in a blinded fashion and will be completed in 7 days.
- At the end of the first week (Week 1 Visit), all patients will be treated with 10 mg/day Lu AF35700 only.
- At visits following the Week 1 Visit, according to the investigator's clinical judgement, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment. This can occur at scheduled or unscheduled visits.

For other patients who can potentially benefit from treatment with Lu AF35700 (Other Patients)

- After the baseline assessment, for eligible patients, the current antipsychotic treatment will be tapered down and completed in 7 days, while the treatment with Lu AF35700 will be initiated at a 10 mg/day dose at Day 1. The 10 mg/day dose will be maintained during the first week of study 16159B.
- At the end of the first week (Week 1 Visit), all patients will be treated with 10 mg/day Lu AF35700 only.
- At visits following the Week 1 Visit, according to the investigator's clinical judgement, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment. This can occur at scheduled or unscheduled visits.

For all patients

- Safety and effectiveness assessments will be performed at the end of Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.
- Patients who complete the 52-week Treatment Period will be contacted for a safety follow-up assessment 6 weeks after the last dose taken.
- If possible, patients who withdraw from the study will be seen for a Withdrawal Visit as soon as possible after they withdraw and will be contacted for a safety follow-up assessment 6 weeks after the last dose of IMP.
- The total study duration per patient from screening to the end of follow-up will be up to 58 weeks for *16159A-patients* and *16323A-patients* and up to 60 weeks for *Other Patients*.
- The study design is presented in Panel 1, the scheduled assessments are summarised in Panel 2, and the treatment regimen is presented in Panel 3.

Target Patient Population

Any patient with schizophrenia who has participated and completed a study investigating the Lu AF35700, can be included in this study, including:

- Patients with treatment resistant schizophrenia (TRS) who completed study 16159A (*16159A-patients*);
- Patients with schizophrenia who completed the dosing period of study 16323A (*16323A-patients*).

In addition, patients who are not experiencing an acute exacerbation, who are currently under antipsychotic treatment and who, according to the investigator's clinical judgement, can potentially benefit from treatment with Lu AF35700 (*Other Patients*), can also be included in this study.

Key Inclusion Criteria

For 16159A-patients

- The patient has completed study 16159A.
- The patient is able to read and understand the *Informed Consent Form*.
- The patient has signed the *Informed Consent Form* specific for study 16159B.
- The patient can potentially benefit from 52-week treatment with Lu AF35700 according to the investigator's clinical judgement.

For 16323A-patients

- The patient has completed the dosing period of study 16323A.
- The patient is able to read and understand the *Informed Consent Form*.
- The patient has signed the *Informed Consent Form* specific study 16159B.
- The patient has a confirmed diagnosis of schizophrenia according to DSM-5™.
- The patient can potentially benefit from 52-week treatment with Lu AF35700 according to the investigator's clinical judgement.

For Other Patients

- The patient has schizophrenia, diagnosed according to DSM-5™.
- The patient is able to read and understand the *Informed Consent Form*.
- The patient has signed the *Informed Consent Form* specific study 16159B.
- The patient is a man or woman, aged ≥18 years.
- The patient has been prescribed oral antipsychotic treatment at the recommended dose range as stated in the SmPC or equivalent document/label for 6 weeks prior to the Screening Visit.
- The patient has a PANSS total score ≥60 and ≤90 at Screening and Baseline Visits.
- The patient has a Clinical Global Impression – Severity of Illness (CGI-S) score ≤4.
- The patient is in need of a change in the current antipsychotic treatment and, according to the investigator's clinical judgement, the patient can potentially benefit from a switch to another treatment including, but not limited to, any of the following reasons:
  - lack of adequate response to his or her current antipsychotic medication;
  - poor tolerability to his or her current antipsychotic medication;
  - unwillingness of the patient to adhere to his or her current antipsychotic medication.

Key Exclusion Criteria

For 16159A-patients

- The patient has been diagnosed with a primary psychiatric disorder other than schizophrenia during study 16159A.
- The patient, in the opinion of the investigator, is at significant risk of suicide, or:
  - Answers "Yes" to any question on the Suicidal Behaviour section of the C-SSRS, OR
  - Answers "Yes" to questions 4 and 5 on the Suicidal Ideation section of the C-SSRS

For 16323A-patients

- The patient has been diagnosed with a primary psychiatric disorder other than schizophrenia during study 16323A.
- The patient, in the opinion of the investigator, is at significant risk of suicide, or:
  - Answers "Yes" to any question on the Suicidal Behaviour section of the C-SSRS, OR
  - Answers "Yes" to questions 4 and 5 on the Suicidal Ideation section of the C-SSRS

For Other Patients

- The patient has any current psychiatric disorder (DSM-5™ criteria) other than schizophrenia established as the primary diagnosis.
- The patient is experiencing acute exacerbation of psychotic symptoms at the Screening Visit, between the Screening and Baseline Visits or at the Baseline Visit.
- The patient is treated with clozapine at the time of the Screening Visit.
- The patient has a substance use disorder which according to the investigator's judgment may compromise the patient's ability to comply with the study procedures, or preclude the benefits of the study medication.
- The patient, in the opinion of the investigator, is at significant risk of suicide, or:
  - Answers "Yes" to any question on the Suicidal Behaviour section of the C-SSRS, OR
  - Answers "Yes" to questions 4 and 5 on the Suicidal Ideation section of the C-SSRS

Investigational Medicinal Products, Doses and Mode of Administration

Lu AF35700 – 10, 20 mg/day; tablets, orally, once daily

Lu AF35700 – 70 mg/week; tablets, orally, once weekly

Tablets will be taken in the morning or evening.

For16159A-patients

- In addition, during the first week of study 16159B, *16159A-patients* will receive (in a blinded fashion) a down-titration wallet from study 16159A.
- For patients who were randomised to risperidone or olanzapine in study 16159A, the discontinuation of risperidone or olanzapine will be done according to the following scheme:
  - Risperidone: 4 mg/day for the first 3 days; 2 mg/day for the 4 subsequent days, encapsulated tablets, orally, once daily
  - Olanzapine: 10 mg/day for the first 3 days; 5 mg/day for the 4 subsequent days, encapsulated tablets, orally, once daily
- For patients who were randomised to Lu AF35700 in study 16159A, the Lu AF35700 encapsulated tablets will be stopped and patients will receive placebo for 7 days, encapsulated tablets, orally, once daily.

For 16323A-patients

- In addition, during the first week of study 16159B, *16323A-patients* will receive (in a blinded fashion) a down-titration wallet from study 16323A.
- For patients who were randomised to quetiapine, the discontinuation of quetiapine will be done according to the following scheme:
  - Quetiapine: 600 mg/day for the first 3 days; 300 mg/day for the 4 subsequent days, encapsulated tablets, orally, once daily.
- For patients who were randomised to Lu AF35700, the Lu AF35700 encapsulated tablets will be stopped and patients will receive placebo for 7 days, encapsulated tablets, orally, once daily.

For Other Patients

- The treatment with Lu AF35700 tablets will be initiated at daily dose of 10 mg at Day 1 of study 16159B, while the discontinuation of the current oral antipsychotic medication will be gradually down-titrated according to the corresponding current SmPC or equivalent document/label and will be completed at Day 7.

For all patients

- Dose adjustments for efficacy or tolerability are allowed according to the investigator's clinical judgement based on the patient's response and tolerability to treatment.

Effectiveness Assessments

- Positive and Negative Syndrome Scale (PANSS)
- 4-item Negative Symptom Assessment (NSA-4)
- Clinical Global Impression – Severity of Illness Scale (CGI-S)
- Quality of Life scale in Schizophrenia (QLS)
- Tolerability and Quality of Life scale (TooL)
- The Readiness for Work Questionnaire (WoRQ)
- Personal and Social Performance scale (PSP)
- Medication Satisfaction Questionnaire (MSQ)
- Health Economics Assessment (HEA)

Pharmacokinetic Assessments and Biobanking

Blood samples will be collected during the study for pharmacokinetic analysis of Lu AF35700 and its metabolite.

Biobanking blood samples will be collected for long term storage and possible future exploratory biomarker research including gene expression profiling, pharmacogenetics, metabolomics/proteomics.

Safety and Tolerabilty Assessments

- Adverse events (AEs)
- Clinical safety laboratory tests
- Vital signs
- Weight/BMI/waist circumference
- Electrocardiograms (ECGs)
- Physical examinations
- Modified Simpson Angus Scale (mSAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Scale (BARS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Serum prolactin, HBA1c, and blood lipid profile

Endpoints

- Primary safety and tolerability endpoints:
  - Adverse events
  - Absolute values, changes values from baseline and potentially clinically significant values in:
    - Clinical safety laboratory tests
    - Body weight, BMI, and waist circumference
    - Vital signs (systolic blood pressure, diastolic blood pressure, and pulse)
    - ECG parameters (ventricular rate, RR, PR, QRS, QT, and QT_{cF})

- Exploratory safety and tolerability endpoints:
  - Mean change from baseline in AIMS, BARS and mSAS total scores
  - C-SSRS categorisation

Endpoints – continued

- Exploratory effectiveness endpoints:
  - Psychotic symptoms
    - Mean change from baseline in PANSS total score
    - Mean change from baseline in PANSS subscale scores (PANSS Negative Symptoms subscale, PANSS Positive Symptoms subscale, PANSS General Psychopathology subscale)
  - Negative symptoms
    - Mean change from baseline in NSA-4 total score
  - Global clinical impression
    - Mean change from baseline in CGI-S score
  - Andreason symptoms remission rate
    - Binary variable (Y/N) of remission rate (simultaneous ratings of mild or less on PANSS specific items: P1, G9, P3, P2, G5, N1, N4, and N6) at Week 52 Visit
  - Quality of life and functioning
    - Mean change from baseline in QLS score
    - Mean change from baseline in TooL score
    - Mean change from baseline in WorQ score
    - Mean change from baseline in PSP total score
  - Treatment satisfaction:
    - Mean change from baseline in MSQ score
  - Health care resource utilisation
    - Health care resource used during 52-week study period

Statistical Methodology

- Safety and effectiveness assessments will be summarised descriptively.
- For *16159A-patients*, summaries will be prepared with respect to 2 baselines: Baseline 2 just prior to randomisation in study 16159A and Baseline in study 16159B. Summaries will be prepared overall and by the previous treatment (treatment group in the studies feeding into this extension study or previous treatment for patients not included in any Lu AF35700 study before).
- Specific tables of adverse events seen shortly after initiation of the weekly dosing regimen will be prepared.
- The statistical methodology will be detailed in a Statistical Analysis Plan.

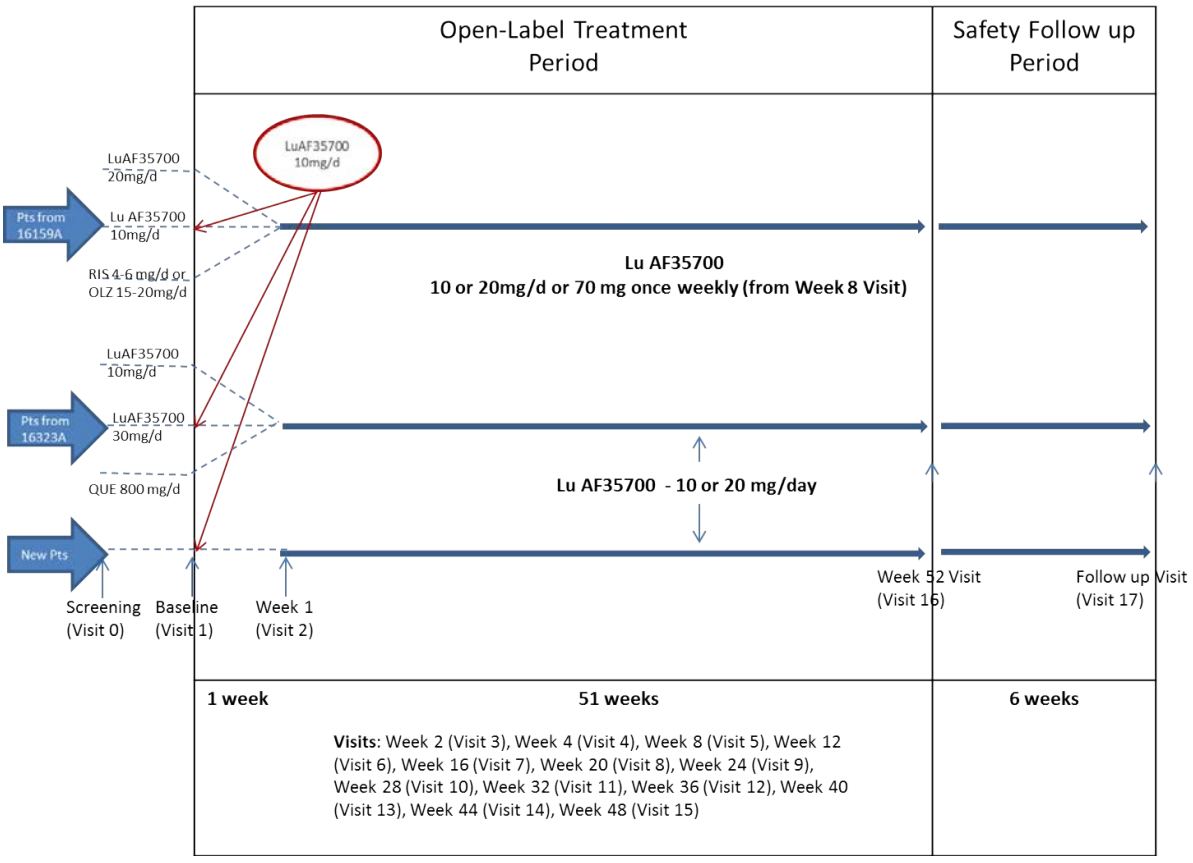
Sample Size Considerations

- No formal sample size calculation has been performed for the present study.
- Approximately 400 patients with schizophrenia are planned to be enrolled in total in order to provide relevant long-term safety data. It is assumed that about 270 patients will come from study 16159A, 30 patients from study 16323A, and an additional 100 patients who need to change their antipsychotic treatment will be included. The distribution of the number of patients may be adjusted based upon the recruitment rate in each group. With approximately 400 patients included, it will be possible to obtain solid information on long-term safety of treatment with Lu AF35700.
- To ensure sufficient exposure to the daily dosing regimen, the number of patients who completed study 16159A and who can be treated with the weekly dosing regimen will be limited to 50 patients.

Ethical Rationale for Study and Study Design

- This open-label long-term study will provide long-term data of Lu AF35700 for the treatment of patients with schizophrenia who have completed studies 16159A or 16323A or for treatment of patients for whom a switch to an antipsychotic treatment with Lu AF35700 can be beneficial according to the investigator's clinical judgement (either due to sub-optimal symptom control or lack of tolerability).
- The design of the study is in accordance with the Declaration of Helsinki (ethical principles for medical research involving human subjects).
- The following aspects of the current study design will serve as safeguards for the safety and well-being of the enrolled patients:
  - At each visit, the investigator will evaluate safety, tolerability, and benefit of treatment, and decide whether the patient will continue in the study.
  - Safety follow-up contact will be performed 6 weeks after the last dose of Lu AF35700 (whether it will be a Primary Outcome or Withdrawal Visit) to ensure a proper follow-up of the enrolled patients.
  - The patient may withdraw from the study at any time, for any reason, specified or unspecified and without penalty or loss of benefits to which the patient is otherwise entitled. Unscheduled visits can be made and immediate withdrawal is possible if his/her condition worsens.
  - The patient will be fully informed about the study including the risks and benefits of his/her participation in the study.

Panel 1 Study Design



Panel 2 Study Procedures and Assessments

Visit	Screening[a]	Baseline[b]	Treatment Period														Primary Outcome or Withdrawal[c]	Safety Follow-Up[d]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
End of Week	**-**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Day	**-14/-7**	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	
Visit Window (days)[e]			**± 3**	**± 3**	**± 3**	**± 6**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**+3**
Baseline Procedures and Assessments																		
Signed informed consent	√[a]	√																
Diagnosis (DSM-5™)	√[a]	√[f]																
Demographics (age, sex, race)	√[a]	√[f]																
Relevant social, medical and psychiatric history	√[a]	√[f]																
Height	√[a]	√[f]																
Inclusion/exclusion criteria	√	√																
Effectiveness Assessments																		
PANSS	√	√[g]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
CGI-S	√	√[g]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
PSP	√	√[g]			√					√							√	
NSA-4		√[g]			√					√							√	
QLS		√[g]			√					√							√	
WoRQ		√[g]			√					√							√	
TooL		√[g]			√					√							√	
MSQ		√[g]			√					√							√	
HEA		√[h]															√	
Pharmacokinetic Assessments																		
Blood sampling for Lu AF35700 and metabolite assay		√[g]			√					√							√	
Translational Medicines Assessments[i]																		
Blood sampling for gene expression profiling (RNA)[j]		√[i]															√[i]	
Blood sampling for metabolomics/proteomics (plasma)[j]		√[i]															√[i]	
Blood sampling for pharmacogenetics (optional)[k]		√[i]																

Visit	Screening[a]	Baseline[b]	Treatment Period														Primary Outcome or Withdrawal[c]	Safety Follow-Up[d]
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
End of Week	**-**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Day	**-14/-7**	**0**	**7**	**14**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	
Visit Window (days)[e]			**± 3**	**± 3**	**± 3**	**± 6**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**+3**
Safety Assessments																		
Adverse events	√	√[l]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√[m]
Blood and urine sampling for clinical safety laboratory tests	√[a]	√[g]			√					√							√	√[n]
Serum prolactin[o]	√[a]	√[g]			√					√							√	
HBA1c (fasting)	√[a]	√[g]			√					√							√	
Fasting blood glucose (P-glucose) and lipid profile (S-cholesterol, S-triglycerides, S-low density lipoprotein (LDL), S-high density lipoprotein (HDL))	√[a]	√[g]			√					√							√	
Vital signs	√	√[g]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
ECGs [p]	√	√[g]			√			√			√			√			√	
Body weight	√	√[g]			√					√							√	
Waist circumference	√	√[g]			√					√							√	
Physical Examination	√[a]	√[g]															√	
Abnormal movements rating scales (AIMS, BARS, mSAS)		√[g]			√					√							√	
C-SSRS	√	√[g]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Other Study Procedures																		
IMP dispensed[q]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√		
Possible change in IMP dose[q]			√	√	√	√	√	√	√	√	√	√	√	√	√	√		
IMP returned and accountability			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Recent and concomitant medication	√	√[s]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Urine drug screen	√[a]	√[t]															√	
Pregnancy test[u]	√[a]	√[g]			√					√							√	

a. Screening Visit will be performed only for newly recruited patients and screening assessments marketed with an "a" will not be repeated at Baseline Visit. *16159A-patients* and *16323A-patients* will proceed from their lead-in study directly to the Baseline Visit. The ICF must be signed before any study related activities take place.

b. For *16159A-patients*, the Baseline Visit will be performed the same day as the Primary Outcome Visit of study 16159A. For *16323A-patients*, the Baseline Visit will be performed the same day as the last day of the dosing period of study 16323A. The inclusion/exclusion criteria are confirmed based on the evaluation of the latest data available in the study 16323A or 16159A as applicable.

c. This visit should take place as soon as possible after the patient withdraws from the study treatment.

d. The Safety Follow-up Visit will be done 6 weeks (+3 days) after the last dose of IMP. This visit can be a telephone contact, unless an SAE has occurred since last visit or unless there was a clinically significant abnormal safety laboratory test value at the last visit. In such cases, safety follow-up(s) must be scheduled to allow for a medical examination and/or blood sampling. Further Safety Follow-up Visits beyond 6 weeks may be needed as judged by the

investigator (if further Safety Follow-up Visits are performed, these must be recorded in the patient's medical record, and not in the CRF).

e. If the date of a patient visit does not conform to the study plan, subsequent visits should be planned to maintain the visit schedule relative to the Baseline Visit. The number of days between 2 visits should not exceed the number of days for which the patient has been dispensed IMP.
f. For *16159A-patients* and *16323A-patients,* the data will be linked respectively from the Screening Visit in the study 16159A eCRF or from the Screening Visit in the study 16323A eCRF, when applicable.
g. For *16159A-patients* and *16323A-patients,* results from effectiveness/safety assessments and blood/urine samples performed respectively at the Primary Outcome Visit (Visit 12) in study 16159A or at the last day of the dosing period (Day 42) in study 16323A (when available) will be linked to the Baseline Visit (Visit 1) in study 16159B, when applicable.
h. For *16159A-patients,* HEA data will be linked from the Baseline A Visit in the study 16159A eCRF.
i. To be performed only for newly recruited patients not previously participating in a study investigating Lu F35700.
j. Exploratory gene expression profiling (RNA) and metabolomics/proteomics are covered by the main Patient Information Sheet.
k. Sampling for pharmacogenetics is optional and a separate Patient Information Sheet covers this analysis. This sampling should preferably be at the Baseline Visit, but may be collected at any visit that includes a clinical safety laboratory sample.
l. For *16159A-patients* and 16323A-patients, ongoing adverse events from study 16159A and 16323A, respectively, are to be transferred by the investigator to the eCRF, when applicable.
m. Only for adverse events ongoing at the Primary Outcome/Withdrawal Visit and new SAEs.
n. Only to be taken if the laboratory test was clinically significantly abnormal at the Primary Outcome/Withdrawal Visit.
o. Prolactin results will remain blinded throughout the study.
p. For *16159A-patients*, additional ECGs will be done; 1 ECG recording before the daily dose is switched to weekly dosing (preferably on the day the decision of switching from daily to weekly dosing is taken) and 1 ECG recording the day after the first weekly dose is taken.
q. The first dose of IMP should be taken after the Baseline Visit is completed. All treatment assignment and subsequent IMP assignment is done via the IVRS/IWRS. The IVRS/IWRS will be assessed at the unscheduled visit only if the dose adjustment requires dispensing of IMP.
r. The dose of IMP can be increased for efficacy or decreased for tolerability at scheduled or unscheduled visits from Week 1 Visit.
s. For *16159A-patients* and 16323A-patients, ongoing concomitant medication in study 16159A and 16323A, respectively, must be transferred by the investigators to the 16159B eCRF. All prescription, non-prescription medications, and herbal medications taken during study 16159B will be recorded as concomitant medications.
t. Urine drug screen tests can be repeated any time during the study at the discretion of the investigator.
u. S-βhCG pregnancy test should be performed at the Screening Visit (Only for *Other-patients)*, Visit 5, Visit 10 and the Primary Outcome/Withdrawal Visit for women of childbearing potential. Urine pregnancy tests can be performed at any time during the study at the discretion of the investigator.

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Appendices

List of Panels

List of Abbreviations and Definitions of Terms

AE	Adverse event
AIMS	Abnormal involuntary movement scale
ALT	alanine aminotransferase
AME	absorption metabolism and excretion
AP	alkaline phosphatase
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under curve
BARS	Barnes Akathisia Rating Scale
BUN	blood urea nitrogen
CAR	conditioned avoidance responding
CGI-S	Clinical Global Impression – Severity of Illness
CIOMS	Council for international Organizations of Medical Sciences
C_{max}	maximum observed concentration
CNV	copy number variation
CPK	creatine phosphokinase
CRA	clinical research associate
CRF	case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FDA	United States Food and Drug Administration
HBA1c	Glycated haemoglobin, Type A1c
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HEA	Health economic assessment
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors

IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
INR	international normalised ratio of prothrombin time
IRB	institutional review board
ISM	international study manager
I-TMF	investigator trial master file
IVRS	interactive voice response system
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LOCF	last observation carried forward
Lu	Lundbeck
MAD	Multiple ascending dose
MMRM	mixed model for repeated measurements
mSAS	Simpson Angus Scale
MSQ	Medication Satisfaction Questionnaire
NOAEL	no-observed-adverse-effect level
NSA-4	4-item Negative Symptom Assesment
PANSS	Positive and Negative Symptom Scale
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
popPK	Population pharmacokinetics
PR	specific ECG interval describing atrioventricular conduction
PRO	patient-reported outcome
PSP	Personal and Social Performance Scale
QLS	Quality of Life Scale
QP	qualified person
QRS	specific ECG interval describing ventricular depolarisation
QT	specific ECG interval describing ventricular depolarisation/repolarisation
QT_c	heart-rate corrected QT interval
QT_{cF}	heart-rate corrected QT interval using Fridericia's correction formula
RR	specific ECG interval describing the ventricular depolarisation/repolarisation cycle
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SNP	single-nucleotide polymorphism
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction

TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed concentration
TMF	trial master file
TooL	Tolerability and Quality of Life
TRS	Treatment-resistant schizophrenia
WoRQ	Readiness for Work Questionnaire

1 Introduction

1.1 Background

1.1.1 Overview

Schizophrenia is a severe, complex, chronic, and disabling psychiatric disorder with a lifetime prevalence of around 1%.[1] Schizophrenia is characterised by profound disturbances in thinking, perception, and emotion and the clinical manifestation of the disease encompasses a wide range of symptoms such as positive symptoms (for example, delusions, hallucinations, and disorganised behaviour), negative symptoms (for example, affective flattening, social withdrawal, anhedonia, and poverty of speech), and symptoms of cognitive impairment (for example, impaired executive functioning, working memory, and attention deficits).

Numerous antipsychotics have been developed which all rely on the same underlying mechanism, namely interfering with dopamine receptors, and more specifically, dopamine D_2 receptor antagonism. Therapies with phenothiazines, such as haloperidol and thiothixene, are effective but induce extra pyramidal symptoms (EPS) such as dystonia, muscle rigidity, tremor, and akathisia.[2] Long-term effects, which develop after months to years of therapy, also include tardive dyskinesia. The above-mentioned drugs are referred to as typical or conventional antipsychotics and the adverse effects appear to be directly related to the dopamine D_2 receptor blockade in the basal ganglia,[3] whereas the antipsychotic effect of these compounds is dependent on reducing dopamine D_2 mediated neurotransmission in the mesolimbic tracts (including the nucleus accumbens, stria terminalis, and the olfactory tubercle).

Lu AF35700 is a novel deuterated compound with affinity for dopaminergic, serotonergic, and α-adrenergic receptors. The receptor binding profile and the pharmacological properties derived from animal experiments indicate that Lu AF35700 possesses antipsychotic activity combined with a benign tolerability profile.

The following sections 1.1.2 to 1.1.6 provide an overview of the nonclinical and clinical data currently available for Lu AF35700. Refer to the *Investigator's Brochure*[4] for more detailed information.

1.1.2 Nonclinical Pharmacology Data

Lu AF35700 is a novel deuterated compound with affinity for serotonergic, dopaminergic, and α-adrenergic receptors, and acts as an antagonist of those receptor types. The multi-receptor profile of Lu AF35700 is believed to have an antipsychotic effect.

Lu AF35700 has similar high affinity for the human serotonergic 5-HT_{2A} and 5-HT_6 receptors. Like "atypical antipsychotics", the affinity for the human 5-HT_{2A} receptor is substantially

higher than for the dopamine D_2 receptor. Distinctively, Lu AF35700 has higher affinity for the human dopamine D_1 receptor than it has for the human dopamine D_2 receptor.

The *in vitro* receptor profile of high affinity for 5-HT_{2A} and 5-HT_6 receptors and low affinity for dopamine D_2 receptors was confirmed by *in vivo* occupancy studies. The predicted steady-state concentration resulting in 50% target occupancy (EC_{50}) was calculated based on *in vivo* occupancy and pharmacokinetic (PK) data from rats. The EC_{50} for 5-HT_6 (12 ng/mL) and 5-HT_{2A} (20 ng/mL) receptors is equipotent and much lower than for dopamine D_1 (115 ng/mL) and dopamine D_2 (255 ng/mL) receptors.

The potent binding to dopamine D_1 receptors combined with a lower affinity for the dopamine D_2 receptors is believed to result in a beneficial efficacy profile and a tolerability profile without the troublesome adverse effects associated with extensive dopamine D_2 receptor blockade, such as extrapyramidal symptoms (EPS), hyperprolactinaemia, sexual dysfunction, and dysphoria/anhedonia. Furthermore, given the lack of muscarinic receptor blockade, it is expected that Lu AF35700 will not have a negative impact on cognitive performance related to muscarinic receptor inhibition.

In animal models, Lu AF35700 inhibited conditioned avoidance responding (CAR), amphetamine-induced hyperactivity, and phencyclidine (PCP)-induced hyperactivity at doses having no sedative or motor inhibiting effects, indicative of antipsychotic potential combined with few side effects.

Lu AF36152 is the major metabolite of Lu AF35700 and has a pharmacological *in vitro* and *in vivo* profile which is similar to that of Lu AF35700 although it is less potent *in vivo*.

1.1.3 Pharmacokinetics and Metabolism in Animals

The absorption, distribution, metabolism, and excretion (ADME) properties of Lu AF35700 have been characterised in the animal species used for safety assessment: Lu AF35700 is well absorbed from the gastrointestinal tract (94% in the rat) and the time to maximum observed concentration (t_{max}) is 0.5 to 1 hour post-dose in rats and dogs. It is distributed throughout all tissues, including the brain. The protein binding of Lu AF35700 is high (95% to 98%) in plasma from mice, rats, rabbits, dogs, and humans. The main route of excretion in rats and dog is via the faeces.

Overall, the metabolic pathways across species are similar and all metabolites observed in humans were observed in at least one animal species used for safety evaluation. Relative abundance measurements in plasma following multiple oral administrations showed that the potential relevant human metabolites have been adequately safety tested in the animal toxicity studies in line with the regulatory recommendations.

[redacted]

1.1.4 Nonclinical Safety Studies

Safety pharmacology studies were conducted with Lu AF35700 to examine the effect on the major physiological functions (central nervous system [CNS], cardiovascular, and respiratory systems) in rats and dogs. The tolerability and toxicity of Lu AF35700 was evaluated by oral treatment for up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in dogs. The potential genotoxicity of Lu AF35700 was evaluated *in vitro* and *in vivo*. The effect of Lu AF35700 on fertility and early embryonic development was assessed in the rat, and foetal developmental toxicity was assessed in rats and rabbits.

Both Lu AF35700 and its major metabolite Lu AF36152 show high affinity to cardiac ion channels in *in vitro* systems. In a manual patch clamp assay, both compounds inhibited the human ether-à-go-go-related gene (hERG) ion channel with concentrations resulting in 50% inhibition (IC_{50}) of 0.060 µM and 0.177 µM for Lu AF35700 and Lu AF36152, respectively.

In dogs, electrocardiogram (ECG) waveform morphology changes (ventricular ectopic beats) were observed in the cardiovascular safety pharmacology study and in the 4-week oral toxicity study but ventricular ectopic beats were not seen in dogs after 13 and 39 weeks of dosing. An increase in QT_c interval was observed at the highest dose during Weeks 6 and 13 in the 13-week oral toxicity study, but QT_c prolongation was not observed in the 39-week toxicity study; although these ECG changes could not be clearly attributed to treatment, a drug-related effect cannot be excluded.

The principal target organs identified in the repeated dose toxicity studies were the central nervous system (clinical observations in mice, rats, and dogs), the rodent mammary gland (prolactin-mediated effects in female mice, male, and female rats), the rodent female reproductive organs (prolactin-mediated effects on uterus in rats, and vagina in mice and rats), the lungs (phospholipidosis in rats), and the heart (ECG changes in dogs).

Lu AF35700 was not genotoxic in standard regulatory *in vitro* and *in vivo* genotoxicity tests.

The no-observed-adverse-effect levels (NOAELs) established in the toxicity studies were 20 (males)/30 (females) mg/kg/day in the mouse, 40 (males)/80 (females) mg/kg/day in the rat, and 3 mg/kg/day in the dog. The overall NOAEL at 3 mg/kg/day Lu AF35700 was established based on a reduced weight gain and an effect on the ECG (QT_c prolongation and ventricular ectopic beats) at the highest dose in dogs.

The behavioural and clinical observations in the animals and the toxicological target organs defined were as predicted from the pharmacological and chemical properties of Lu AF35700. Apart from the potential risk of ECG changes, no other effects of Lu AF35700 are considered relevant for humans at exposure levels corresponding to those achieved the highest dose

tested in the mouse, rat and dog. Please refer to the *Investigator's Brochure*[4] for the exposure ratios.

It is concluded that the toxicological effects of Lu AF35700 were well characterised in the toxicology, genotoxicity, and reproductive toxicology studies and the results support that Lu AF35700 can safely be administered to humans at the proposed dose levels.

1.1.5 Clinical Data

1.1.5.1 Overview of Studies

Currently, three studies with Lu AF35700 have been completed in healthy subjects (studies 14198A, 15867A, and 15868A). One study in patients has been completed experimentally (study 14754A). Finally, two studies are ongoing (studies 15859A and 16156A). As of August 2015, a total of 74 healthy subjects and 84 patients with schizophrenia have been exposed to Lu AF35700.

The completed studies in healthy subjects (all men) comprise the first-in-human (FIH) study, an AME study, and a PET study. In the FIH study, 6 subjects received a single 10 mg dose and 20 subjects received 3 mg Lu AF35700 together with 3 mg of a non-deuterated Lu AF35700 analogue once daily for 18 days. In each of the AME and PET studies, 6 subjects received a single dose of 30 mg Lu AF35700. Based on these studies, Lu AF35700 was safe and well tolerated.

A multiple-ascending-dose (MAD) study in 96 patients with schizophrenia has been completed experimentally and preliminary unblinded data are included in this document. The study was a double-blind, placebo-controlled study with 10 cohorts of up to 10 patients each. The treatment duration was 21 days in all cohorts. In Cohorts 1 to 7, collectively referred to as Part A, male patients received daily doses of 5, 7.5, 11, 16, 20, or 30 mg/day. In Cohorts 1 to 6, the patients were randomised (7 to 3, respectively) to receive oral solutions of Lu AF35700 or placebo, and in Cohort 7, all patients received a 20 mg Lu AF35700 tablet (one-half of the patients in this cohort received the tablet in a fasted state and the other half received the tablet in a fed state). In Cohort 8, the sole cohort in Part B, women with schizophrenia were randomised (7 to 3, respectively) to receive an oral solution of Lu AF35700 or placebo. In Cohorts 9 and 10, collectively referred to as Part C, male and female patients were randomised (7 to 3, respectively) to receive oral solutions of 45 mg (Cohort 9) or 75 mg (Cohort 10) Lu AF35700 or placebo once weekly. In all cohorts, patients who received doses ≥20 mg were up-titrated; refer to the *Investigator Brochure*[4] for detailed information about the titration schedules used in each cohort.

Study 15859A is an ongoing open-label PET study investigating the occupancy-plasma-concentration relationship of the D_1, D_2, and 5-HT_6 receptors in men with schizophrenia. The occupancy-plasma-concentration relationship for each of the D_1, D_2, and 5-HT_6 receptors is investigated in a separate group. In each of the D_1, D_2, and 5-HT_6 groups, up to four sequential cohorts of 2 patients each, receive Lu AF35700 doses for up to 21 days starting at

10, 20, and 10 mg/day, respectively, in the first cohort. The doses in subsequent cohorts are adjusted based on the occupancy data.

Study 16156A is an ongoing randomised, double-blind, parallel-group, placebo-controlled single- and multiple-dose study investigating the safety, tolerability, and PK properties of Lu AF35700 in healthy Japanese and Caucasian men. The study consist of three parts: Part A, in which Japanese and Caucasian men receive a single dose of 5 mg Lu AF35700; Part B, in which Japanese men receive a single dose of 10 mg Lu AF35700; and Part C, in which Japanese and Caucasian men receive a dose of 10 mg/day Lu AF35700 for 5 days.

1.1.5.2 Pharmacokinetics

A preliminary integrated popPK analysis was performed on data from studies 14198A, 14754A, 15867A, and 15868A.

In the popPK model, the absorption phase was adequately described by first-order absorption (absorption rate constant [k_a] = 0.27 L/h) with lag-time (1 h). The distribution profiles of both Lu AF35700 and Lu AF36152 were best described by two-compartment models with central and peripheral compartments. The population volume of distribution of Lu AF35700 and Lu AF36152 was estimated to 5442 and 4933 L, respectively. Plasma protein binding was investigated *in vitro* in human plasma and, overall, Lu AF35700 was classified as "highly" protein bound (95% to 99%). The apparent oral clearance of Lu AF35700 and Lu AF36152 was estimated to 29 L/h and 15 L/h, respectively. From the population estimates, the elimination half-life for Lu AF35700 and Lu AF36152 was estimated to 143 hours and 250 hours, respectively.

Preliminary results from the MAD study indicate that for the patients receiving therapeutically relevant doses of Lu AF35700, the parent compound at Day 21/24 had a median t_{max} of 8 hours, mean C_{max} ranging from 24.6 to 43.8 ng/mL, and mean area under the curve from zero to 24 hours ($AUC_{0\text{-}24h}$) ranging from 455 to 759 ng·h/mL. For the major metabolite Lu AF36152, the corresponding values were a median t_{max} ranging from 9 to 14 hours, mean C_{max} ranging from 25.2 to 43.8 ng/mL, and mean $AUC_{0\text{-}24h}$ ranging from 475 to 685 ng·h/mL.

Please refer to the *Investigator's Brochure*[4] for a summary of PK parameters.

1.1.5.3 Safety

The main body of safety data in patients with schizophrenia comes from the MAD study (study 14754A) which has been completed. The other study in patients with schizophrenia, the ongoing PET study (study 15859A), is still blinded.

In the MAD study, the adverse events with the highest incidence (>10%) in the Lu AF35700 groups in the daily dosing cohorts were: somnolence (33%), anxiety (23%), headache (21%, placebo level), orthostatic hypotension (19%), dizziness (16%), psychotic disorder (14%), and akathisia (11%). In the once-weekly dosing cohorts the adverse events occurring in

≥2 patients in the Lu AF35700 groups were (number of patients out of 12): somnolence (5), constipation (4), insomnia (3), anxiety (2), and musculoskeletal pain (2). In total there was 1 serious adverse event, increased psychosis, which necessitated hospitalisation of the patient. The patient recovered after 9 days after treatment with paliperidone. The investigator assessed the causality as *not related* to the investigational medicinal product (IMP). All non-serious adverse events were of *mild* to *moderate* intensity, with the exception of one event of *severe* somnolence which resolved after a few hours. The blinded data from the ongoing PET study showed that anxiety, insomnia, and headache have been reported as adverse events in that study.

Please refer to the *Investigator Brochure*[4] for a summary of the TEAEs with the highest incidence in MAD study 14754A.

In the MAD study, an explorative analysis of the effect of treatment on QT_{cF} indicated a treatment and dose-related trend for QT_{cF} prolongation. None of the patients in the study had any symptoms or QT_{cF} values that met the potentially clinically significant (PCS) criterion (>500 ms or >60 ms increase from baseline) and no observations from ECG or cardiac telemetry were reported as adverse events.

In the MAD study, in the cohorts with the daily dosing regimen, an increase n creatine phosphokinase (CPK) value was observed in the Follow-up Period on assessment days immediately after the termination of Lu AF35700 treatment or one week thereafter. The increase occurred in all Lu AF35700 dosing groups and was greatest (descending order) in the cohorts where patients received 20, 5, and 16 mg/day. The median CPK values were within the reference range (for men: 60 to 400 IU/L) and never >320 IU/L. The cohort in which women were treated with Lu AF35700 showed no increase in CPK values during the treatment period. The fractionated CPK analysis showed that the post-treatment increased CPK values were derived from muscle tissue. In the cohorts with the once-weekly dosing regimen, there were no apparent treatment or dose-related trends in mean or individual CPK values. There were no apparent treatment or dose-related trends in mean or individual data for any of the other clinical laboratory parameters.

In the MAD study, the safety and tolerability was not influenced by the formulation (oral solution *versus* tablet) or the sex of the patient.

The total number of healthy subjects (74) who have received Lu AF35700 is lower than that for patients (84) and they have generally been exposed to lower doses of Lu AF35700 for shorter duration. However, the most frequently reported adverse events in healthy subjects (somnolence, fatigue, headache, and dizziness) were similar to those in patients.

Based on safety and tolerability data from the single-dose PET and AME studies (studies 15867A and 15868A) and the FIH study in healthy subjects (study 14198A), and the MAD study in patients with schizophrenia (study 14754A), a single dose of up to 30 mg Lu AF35700 and multiple doses in the dose range 5 to 30 mg/day or 45 or 75 mg once weekly for 21 days, are safe and well tolerated.

1.1.6 Target Occupancy

A Lu AF35700 PET study (study 15868A) was conducted in 6 young healthy men to characterise the relationship between the combined plasma concentration of Lu AF35700 and Lu AF36152 and the D_2 receptor occupancy using [^{11}C]-PHNO at different time points from 8 to 126 hours after dosing.[5] A pharmacokinetic/pharmacodynamic (PK/PD) model was established to predict the relationship between plasma exposure of Lu AF35700/Lu AF36152 and striatal D_2 dopamine receptor occupancy. Two E_{max} models were combined with simulated plasma concentrations of Lu AF35700 and Lu AF36152 when dosing 10 mg and 20 mg Lu AF35700 QD for 12 weeks. After 5 weeks of daily doses of 10 mg and 20 mg, the contribution of both Lu AF37500 and Lu AF36152 are expected to result in a 48% and 65% D_2 receptor occupancy, respectively.[6]

1.2 Rationale for the Study

The current phase III study, in conjunction with other studies, is part of the LuAF35700 clinical development programme that is designed to evaluate the safety and efficacy of Lu AF35700 for the treatment of adults with schizophrenia.

The design of the current study is in accordance with EMA draft Guideline on clinical investigation of medicinal products in the treatment of schizophrenia.[7] This open-label extension study will provide long-term data of Lu AF35700 for the treatment of patients with schizophrenia.

Blood samples will be collected in an attempt to increase the understanding of the pharmacokinetic properties of Lu AF35700, and its metabolite (Lu AF36152).

2 Objectives

Primary Objective

- To evaluate the safety and tolerability of the long-term treatment with Lu AF35700

Exploratory Objective(s)

- to evaluate the long-term safety and tolerability of daily and weekly doses of Lu AF35700 in patients with schizophrenia during the 52-week treatment period
- to evaluate the therapeutic effect of daily and weekly doses of Lu AF35700 in patients with schizophrenia over a period of 52 weeks on:
  - psychotic symptoms
  - negative symptoms
  - global clinical impression
  - remission rate
  - quality of life and functioning

- treatment satisfaction
- resource utilisation

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[8]

This is an interventional, open-label, flexible-dose, long-term safety study.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*[9] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

Any patient with schizophrenia, who has participated and completed a study investigating Lu AF35700, can be included in this study. In addition, patients who are not experiencing an acute exacerbation, who are currently under antipsychotic treatment and who, according to the investigator's clinical judgement, can potentially benefit from treatment with Lu AF35700, can also be included in this study.

The total study duration per patient from screening to safety follow up will be up to 60 weeks.

The study will consist of 3 periods:
- Screening period – up to 2 weeks (only for patients not previously participating in a study investigating Lu AF35700)
- Treatment period – 52 weeks
- Safety follow up period – 6 weeks

Only the patients not previously participating in a study investigating Lu AF35700 will enter this study at the Screening Visit, for a screening period of up to 14 days to assess eligibility. Patients previously participating in a study investigating Lu AF35700 will enter this study directly at the Baseline Visit.

120 sites are planned in approximately 15 countries (in-/out-patient clinics). The selected sites will be the sites which participated in studies investigating Lu AF35700 including and not limited to the studies 16159A and 16323A (cardiac study).

Approximately 400 patients with schizophrenia are planned to be enrolled with the following assumptions: approximately 270 patients who will have completed the study 16159A, approximately 30 patients who will have completed the dosing period of the study 16323A and approximately 100 additional patients who will need to change their antipsychotic treatment. The distribution of the number of patients may be adjusted upon the recruitment rate in each group.

All eligible patients will be initiated on a daily dose of 10 mg Lu AF35700 at Day 1. Patients previously treated with another antipsychotic than Lu AF35700 will initiate down-titration of their current treatment at Day 1.

At the end of the 1st week (Week 1 Visit), all patients included in this long-term safety study 16159B will be treated with one antipsychotic, Lu AF35700 at daily dose of 10 mg. At visits following the Week 1 Visit, according to the investigator's clinical judgement, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment.

Patients previously participating in a study investigating Lu AF35700 will receive a down-titration wallet from the previous study. The down-titration will be done in a blinded fashion and will be completed at Day 7.

For patients who can potentially benefit from treatment with Lu AF35700 the discontinuation of the current oral antipsychotic medication will be gradually down-titrated according to the corresponding current SmPC or equivalent document/label and will be completed at Day 7.

Only for patients who completed the 16159A study; at the end of the 8th week (Week 8 Visit), according to the investigator's clinical judgment, the treatment with Lu AF35700 daily dosing regimen can be switched to a weekly 70 mg Lu AF35700 dosing regimen. The first weekly tablet will be taken 7 days after the last daily tablet. Thereafter, the switch from Lu AF35700 daily dosing regimen to Lu AF35700 weekly dosing regimen can be performed at any consecutive visit according to the investigator's clinical judgment. The first weekly tablet will be taken 7 days after the last daily tablet. The treatment with Lu AF35700 weekly dosing regimen can be switched back to daily dose of 10 mg for tolerability reasons or to daily dose of 20 mg for worsening of the patient's clinical status. This can occur at scheduled or unscheduled visits. The first daily tablet will be taken 7 days after the last weekly tablet.

The adjustment of Lu AF35700 dosing regimen (10 mg/day or 20 mg/day) will be left to the investigator's clinical judgement. The number of patients under weekly dosing regimen will be limited to 50 patients by the IVRS/IWRS.

All patients, including patients who withdraw, will be scheduled for a Safety Follow-Up Visit 42 days after last dose of IMP.

An internal Safety Committee at H. Lundbeck A/S has been established for Lu AF35700 and the committee will perform regular evaluations of the safety data.

No interim analysis is planned.

After completion of the study, the patients will be treated according to normal practise.

3.2 Rationale for the Study Design

The open-label, flexible-dose, long-term safety study design aims to obtain information on the long-term safety and tolerability of Lu AF35700, a new potential treatment for Schizophrenia

as it is intended to be used in clinical practice. The 52-week treatment period is considered to be of adequate length to determine the sustained safety, tolerability and antipsychotic effectiveness of Lu AF35700.

All patients with treatment resistant schizophrenia who completed study 16159A are eligible to participate in this study. This will enable treatment continuity for patients that received treatment with Lu AF35700, as well as, for patients treated with risperidone or olanzapine in study 16159A the opportunity to derive the possible benefits of treatment with Lu AF35700 for 52 weeks. In addition, all patients with schizophrenia who completed study 16323A, a cardiac safety study, are also eligible to participate in this study and will receive treatment with Lu AF35700. Finally, patients with schizophrenia in need of change in antipsychotic treatment will also be eligible to participate in this study, to have the opportunity to benefit from the possible benefits of Lu AF35700.

The doses of Lu AF35700 to be used in this study were selected based on the aggregate safety, efficacy, pharmacokinetic profile and receptor occupancy data. Daily doses of 10 and 20 mg are estimated to include the therapeutic dose range of Lu AF35700 tested in study 16159A. In addition, taking advantage of the long half-life of Lu AF35700 a once-weekly dose of 70 mg will also be tested. The rationale for testing the safety, tolerability, and effectiveness of a weekly dosing is to explore the feasibility of such a dosing scheme for maintenance dosing; which could result in potential benefits to treatment adherence; which is an issue of considerable interest in patients with schizophrenia.

Safety and tolerability will be assessed by means of withdrawal, reported adverse events, vitals signs, weight, clinical safety laboratory tests, ECGs, and physical examinations. Metabolic adverse events including body weight gain, dyslipidemia, and hyperglycemia are adverse events associated with antipsychotic treatment and represent an important long-term safety risk.[10] The primary variables for assessing those parameters include body weight/BMI, waist circumference, fasting plasma glucose, glycosylated haemoglobin [HbA1c] and lipids (triglycerides, total cholesterol, low-density lipoprotein [LDL], and high density lipoprotein [HDL] cholesterol).

The long-term efficacy will be explored based on the PANSS[11] a well established scale for assessing severity of the symptoms of schizophrenia. The CGI-S[12] will be used as an additional exploratory efficacy measure of clinical response to treatment. The exploratory assessment of the severity of the negative symptoms of schizophrenia will be done using the NSA-4.[13]

Improvement in functional outcome and quality of life are important treatment goals in the long-term management of patients with schizophrenia. In the current study, effects on functional outcomes will be explored using clinician-reported outcomes such as the PSP,[14] QLS[15] and WoRQ.[16]

Taking into account the substantial health economic burden of schizophrenia, the effect of the Lu AF35700 on subjective well-being, treatment satisfaction, disability and health care resource utilisation will be explored. These will be assessed in the study through patient reported outcomes such as MSQ,[17] TooL[18] and HEA.

4 Ethics

4.1 Ethical Rationale

Schizophrenia is a severe, complex, chronic, debilitating, and disabling mental disorder with a poor prognosis. Despite the availability of numerous treatment options, individual response to antipsychotic medication is generally sub-optimal and variable. The majority of patients does not adequately respond to treatment and studies have indicated that only around 10% of the patients with schizophrenia achieve functional remission.[19] The tolerability of the current antipsychotic medications is also limited by numerous adverse events, which hampers the treatment adherence, and in turn, the overall outcome of the treatment. Thus, it is clear that the current treatment options for schizophrenia are far from ideal and development of better therapies for this indication should be an important priority.

The dose regimen of 10, 20 mg/day and 70 mg/week of Lu AF35700 were determined to be safe and well tolerated in the ongoing phase I programme in patients with schizophrenia and elicited the targeted range of D2 receptor occupancy in healthy volunteers (see *Investigator's Brochure*).[4]

This open-label long-term study will provide long-term data of Lu AF35700 for the treatment of patients with schizophrenia who have completed a study investigating Lu AF35700 or for patients for whom a switch to an antipsychotic treatment with Lu AF35700 can be beneficial according to the investigator's clinical judgement (either due to sub-optimal symptom control or lack of tolerability).

The design of the current study is in accordance with the Declaration of Helsinki (ethical principles for medical research involving human subjects).

The following aspects of the current study design will serve as safeguards for the safety and well-being of the enrolled patients:

- At each visit, the investigator will evaluate safety, tolerability, and benefit of treatment, and decide whether the patient will continue in the study.
- Safety follow-up contact will be performed up to 6 weeks after the last dose of Lu AF35700 (whether it will be a Primary Outcome or Withdrawal Visit) to ensure a proper follow-up of the enrolled patients.
- The patient may withdraw from the study at any time, for any reason, specified or unspecified and without penalty or loss of benefits to which the patient is otherwise entitled. Unscheduled visits can be made and immediate withdrawal is possible if his/her condition worsens.

The patient will be fully informed about the study including the risks and benefits of his/her participation in the study. Patients entering this study after having completed a study investigating Lu AF35700 should be informed about this study as early as possible during their participation in the previous study investigating Lu AF35700. In accordance with *Good Clinical Practice,*[9] qualified medical personnel at Lundbeck will be readily available to advise on study-related medical questions. Medical monitoring will be performed throughout the

study. Safety data will be reviewed regularly by the Lundbeck Lu AF35700 Safety Committee to ensure that prompt action is taken, if needed, to maximise patient safety.

In accordance with *Good Clinical Practice,*[9] the investigator will be responsible for all study-related medical decisions.

The consent procedures described above will only be implemented if allowed by local law and regulations and will only be initiated after appropriate approval by the relevant ethics committees.

4.2 Informed Consent

For patients not previously participating in a study investigating Lu AF35700, written informed consent must be obtained before the Screening Visit in this study. For patients previously participating in a study investigating Lu AF35700, written informed consent must be obtained before the Baseline Visit in this study.

No study-related procedures, including any screening procedures, may be performed before the investigator has obtained written informed consent from the patient and/or his or her legal representative (if applicable).

Changing (for example, discontinuing or down-tapering) a patient's concomitant medications prior to the Screening Visit to ensure that the patient meets the selection criteria is a study-related activity and must not occur before the *Informed Consent Form* has been signed.

As fasting samples are to be taken at the Screening Visit, the *Informed Consent Form* must be signed a suitable number of days before the Screening Visit.

If the informed consent process may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the site delegation log.

The Investigator must exclude any adult patient who lacks capacity to consent for himself/herself from participation in the study.The investigator must identify vulnerable patients, that is, patients whose willingness to participate in this study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Patients thus identified must be excluded from participation in the study.

Prior to obtaining written informed consent, the investigator or a designee must explain to the patients and their legal representatives (if applicable) the aims, methods, and potential hazards of the study and any discomfort it may entail. The patients and their legal representatives (if applicable) must be informed that their participation in the study is voluntary and that they are free to withdraw from the study at any time without justifying their decision. The patients and their legal representatives (if applicable) must be informed of the possibility of withdrawing consent (section 8.4).

The patients and their legal representatives (if applicable) must be given ample time and opportunity to enquire about details of the study prior to deciding whether to participate in the study.

The *Informed Consent Form* includes a statement whereby the patient agrees to communicate with their regular doctor of their participation in the study. If the patient does not want his/her regular doctor to be contacted and there is no other way to verify or establish that the patient qualifies for the study, the patient should not be enrolled.

It is the responsibility of the investigator to ensure that all questions about the study are answered to the satisfaction of the patients and their legal representatives (if applicable). Prior to including a patient in the study, an *Informed Consent Form* must be signed and dated by the patient and his or her legal representative (if applicable) and signed and dated by the investigator or a designee. The patients and their legal representatives (if applicable) must receive a copy of the written information (*Patient Information Sheet*) as well as a copy of the signed *Informed Consent Form*.

The consent procedures described above will only be implemented if allowed by local law and regulations and will only be initiated after approval by the relevant ethics committees (IECs) or institutional review boards (IRBs).

The blood samples for exploratory biomarker analysis may be shared with academic or public institutions; however, Lundbeck will remain full control of the samples and their use on accordance with the information in the *Patient Information Sheet* and a material transfer agreement.

4.3 Personal Data Protection

In accordance with European Union Directive 95/46/EC,[20] the data will be processed in accordance with the specifications outlined by the Danish Data Protection Agency to ensure that requirements regarding personal data protection are met. If an external organisation will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organisation to ensure compliance with the above-mentioned legislation.

If applicable, the participation of patients in this study will be reported to the appropriate local data protection agencies, in accordance with European Union Directive 95/46/EC and country-specific guidelines and laws.

4.4 Independent Ethics Committee(s) (IEC(s)) and Institutional Review Board(s) (IRB(s))

This study will be conducted only after approval of the protocol has been granted by the appropriate IEC or IRB and a copy of the written approval has been received by Lundbeck.

The investigator must not screen or include any patients before receiving written approval from the IEC or IRB.

The IEC or IRB must be informed when specific types of protocol amendments have been made and must be asked whether a re-evaluation of the ethical aspects of the study is necessary.

If applicable, interim reports on the study and reviews of its progress will be submitted to the IEC or IRB by the investigator at intervals stipulated in its guidelines.

4.5 Regulatory Approval/Notification Requirements

In accordance with local requirements, this study will be submitted to the regulatory authorities for approval or notification. The study will only be undertaken when Lundbeck has received written approval or confirmation of notification from the regulatory authorities.

5 Study Population

5.1 Numbers of Patients and Sites

Planned regions:
North America, Europe and South America

Approximately planned number of patients:

to be enrolled:	400
to complete the study:	200

Approximately planned number of:

study sites:	120

5.2 Recruitment of patients who can potentially benefit from treatment with Lu AF35700

The recruitment of patients who can potentially benefit from treatment with Lu AF35700 can start in a given site only after the recruitment of the patients in the study 16159A or in the study 16323A is completed.

Competitive patient recruitment between countries and sites will be used during the entire recruitment period to ensure that the required number of patients is enrolled within the planned recruitment period.

The investigators will be notified immediately when the recruitment period comes to an end.

5.3 Selection Criteria

Patient selection to study 16159B is based on the inclusion and exclusion criteria listed below.

Patients who meet each of the inclusion criteria at the Screening Visit (unless otherwise specified) and none of the exclusion criteria at the Screening Visit (unless otherwise specified) are eligible to participate in this study.

Inclusion Criteria

For patients who completed study 16159A

Patients who meet each of the inclusion criteria and none of the exclusion criteria at the Baseline Visit (unless otherwise specified; some criteria assessed as part of the Primary Outcome Visit in study 16159A) are eligible to participate in this study.

1. The patient has completed study 16159A.
2. The patient is still capable of communicating with the site personnel.
3. The patient and if applicable his or her legal representative is/are able to read and understand the *Informed Consent Form*.
4. The patient and if applicable his or her legal representative has/have signed the *Informed Consent Form* for study 16159B.
5. The patient is willing and able to attend study appointments within the specified time windows.
6. The patient can potentially benefit from 52-week treatment with Lu AF35700 according to the investigator's clinical judgment.
7. The patient has a caregiver or an identified responsible person considered reliable by the investigator (for example, family member, social worker, case worker, or nurse) considered reliable by the investigator in providing support to the patient to ensure compliance with study treatment, outpatient visits, and protocol procedures.
8. The patient has a stable living environment, as demonstrated by the ability to provide contact information for themselves and/or family/friend(s)/caregiver(s).
9. The patient, if a woman, must:

- agree not to try to become pregnant during the study, AND
- use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence, vasectomised partner), OR
- have had her last natural menstruation ≥28 months prior to the Primary Outcome Visit in study 16159A, OR
- have been surgically sterilised prior to the Primary Outcome Visit in study 16159A, OR
- have had a hysterectomy prior to the Primary Outcome Visit in study 16159A.

10. The patient, if a man, must:

- use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥3 months after the last dose of IMP, OR

– have been surgically sterilised prior to the Primary Outcome Visit in study 16159A.

The following assessments from the Primary Outcome Visit in study 16159A will be linked to the Baseline Visit: PANSS, CGI-S, PSP, NSA-4, QLS, TooL, MSQ, WorQ, HEA, ongoing adverse events, physical examination, waist circumference, weight, vital signs, 12-lead ECG, mSAS, AIMS, BARS, C-SSRS, ongoing concomitant medication, clinical safety laboratory data (including S-βhCG pregnancy test, HBA1c, blood lipid profile) (see Panel 2).

Additionally, diagnosis, demographics, relevant medical, psychiatric and social history and height will be linked from the Screening Visit in study 16159A to Baseline Visit in this study.

For patients who completed the dosing period of study 16323A

Patients who meet each of the inclusion criteria and none of the exclusion criteria at the Baseline Visit (unless otherwise specified; some criteria assessed as part of the last visit of the dosing period in study 16323A) are eligible to participate in this study.

1. The patient has completed the dosing period of study 16323A.
2. The patient is still capable of communicating with the site personnel.
3. The patient and if applicable his or her legal representative is/are able to read and understand the *Informed Consent Form*.
4. The patient and if applicable his or her legal representative has/have signed the *Informed Consent Form* for study 16159B.
5. The patient is willing and able to attend study appointments within the specified time windows.
6. The patient can potentially benefit from 52-week treatment with Lu AF35700 according to the investigator's clinical judgment.
7. The patient has a caregiver or an identified responsible person considered reliable by the investigator (for example, family member, social worker, case worker, or nurse) considered reliable by the investigator in providing support to the patient to ensure compliance with study treatment, outpatient visits, and protocol procedures.
8. The patient has a stable living environment, as demonstrated by the ability to provide contact information for themselves and/or family/friend(s)/caregiver(s).
9. The patient, if a woman, must:
   – agree not to try to become pregnant during the study, AND
   – use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence, vasectomised partner), OR
   – have had her last natural menstruation ≥28 months prior to the Primary Outcome Visit in study 16323A, OR
   – have been surgically sterilised prior to the last visit of the dosing period in study 16323A, OR
   – have had a hysterectomy prior to the last visit of the dosing period in study 16323A.

10. The patient, if a man, must:
    - use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥3 months after the last dose of IMP, OR
    - have been surgically sterilised prior to the last visit of the dosing period in study 16323A.
11. The patient has a confirmed diagnosis of schizophrenia according to DSM-5™.
12. The patient is willing to discontinue all prohibited psychotropic medications to meet protocol-required washout prior and during the study.

For patients who can potentially benefit from treatment with Lu AF35700

Patients who meet each of the inclusion criteria at the Screening and Baseline Visits (unless otherwise specified) and none of the exclusion criteria at the Screening and Baseline Visits (unless otherwise specified) are eligible to participate in this study.

1. The patient is capable of communicating with the site personnel.
2. The patient and if applicable his or her legal representative is/are able to read and understand the *Informed Consent Form*.
3. The patient and if applicable his or her legal representative has/have signed the *Informed Consent Form* for study 16159B.
4. The patient is willing and able to attend study appointments within the specified time windows.
5. The patient is either an inpatient at a psychiatric setting or outpatient consulting a psychiatrist.
6. The patient has schizophrenia, diagnosed according to DSM-5™.
7. The patient is a man or woman, aged ≥18 years.
8. The patient has been prescribed an oral antipsychotic treatment at recommended dose range as stated in the SmPC or equivalent document/label for 6 weeks prior the Screening Visit.
9. The patient has a PANSS total score of ≥60 and ≤90 at Screening and Baseline Visits.
10. The patient has a Clinical Global Impression-Severity of Illness (CGI-S) score ≤4
11. The patient is in need of a change in the current antipsychotic treatment and according to the investigator's clinical, the patient would potentially benefit from a switch to another treatment, including but not limited to any of the following reasons:
    - lack of adequate response to his or her current antipsychotic medication,
    - poor tolerability to his or her current antipsychotic medication,
    - unwillingness of the patient to adhere to his or her current antipsychotic medication.
13. The patient is willing to discontinue all prohibited psychotropic medications to meet protocol-required washout prior and during the study.
14. The patient has a caregiver or an identified responsible person (for example, family member, social worker, case worker, or nurse), considered reliable by the investigator in providing support to the patient to ensure compliance with study treatment, outpatient visits, and protocol procedures.

15. The patient has a stable living environment, as demonstrated by the ability to provide contact information for themselves and/or family/friend(s)/caregiver(s).
16. The patient, if a woman, must:

- agree not to try to become pregnant during the study, AND
- use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence, vasectomised partner), OR
- have had her last natural menstruation ≥12 months prior to the Screening Visit, OR
- have been surgically sterilised prior to the Screening Visit, OR
- have had a hysterectomy prior to the Screening Visit

17. The patient, if a man, must:

- use 2 methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥1 month after the last dose of IMP, OR
- have been surgically sterilised prior to the Screening Visit

Exclusion Criteria

For patients who completed study 16159A

General

1. The patient has previously been screened in this study.
2. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
3. The patient has developed a severe drug allergy or hypersensitivity to the IMP or its excipients during study 16159A.
4. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

Psychiatric

5. The patient has been diagnosed with a primary psychiatric disorder other than schizophrenia during study 16159A.
6. The patient has a clinically significant unstable illness diagnosed during study 16159A.
7. The patient is experiencing an acute exacerbation of his/her psychotic symptoms according to the investigator's clinical judgement.
8. The patient has a current diagnosis of substance use disorder according to DSM 5™ criteria during study 16159A with the exception of tobacco, or mild cannabis or mild alcohol use disorder. Patients with a positive drug screen test at the Baseline Visit, with the exception of cannabis and verified by repeated testing, are excluded from the study.
9. The patient, in the opinion of the investigator, is at significant risk of suicide, or the patient:

- Answers "Yes" to any question on the Suicidal Behaviour section of the C-SSRS, OR
- Answers "Yes" to questions 4 and 5 on the Suicidal Ideation section of the C-SSRS.

10. The patient has started formal cognitive or behavioural therapy or systematic psychotherapy during study 16159A. Any ongoing formal psychotherapy initiated more than 6 weeks prior to Screening Visit of study 16 159A should be continued with the same methodology and at the same frequency and intensity during the entire study.
11. The patient has experienced neuroleptic malignant syndrome during study 16159A.

Medical

12. The patient has any other medical disease for which the treatment takes priority over treatment of schizophrenia or is likely to interfere with study treatment or impair treatment compliance.
13. The patient has a moderate or severe ongoing adverse event related to IMP from study 16159A considered of potential safety risk by the investigator.
14. The patient takes or has taken disallowed recent or concomitant medication (specified in Appendix II) in study 16159A.
15. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability or efficacy, or interfere with the conduct or interpretation of the study.
16. The patient has clinically significant abnormal vital signs considered of potential safety risk by the investigator.
17. The patient has one or more laboratory values outside the reference range, based on the last available blood or urine samples taken during study 16159A that are, in the investigator's opinion, of potential risk to the patient's safety, or the patient has any of the following values at study 16159A (the medical monitor should be contacted in case of uncertainty):
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
18. The patient has not previously been diagnosed with diabetes, but meets ANY of the following criteria (newly diagnosed diabetes) based on the last available blood samples taken during study 16159A:
    - HbA1C >6.5%, OR
    - fasting plasma glucose >126 mg/dL (7.0 mmol/L), OR
    - non-fasting plasma glucose >200 mg/dL (11.1. mmol).
19. The patient has previously been diagnosed with diabetes, but the condition is unstable as determined by ANY of the following criteria based on the last available blood samples taken during study 16159A:
    - HbA1c ≥7.0%, OR
    - glucose >6.94 mmol/L (fasting, >125 mg/dL) or 11.1 mmol/L (nonfasting, 200 mg/dL)

- any other abnormal laboratory tests that in the investigator's clinical judgement are medically significant and would impact on the safety of the patient or the interpretation of the study results.

20. The patient has orthostatic hypotension (defined as a decrease in systolic blood pressure >20 mmHg between two measurements, first in the supine position and then sitting, and standing after the patient has rested in each position for at least 3 minutes.
21. The patient has, based on the last available ECG measurement taken during study 16159A:
    - an abnormal ECG that is, in the investigator's opinion, clinically significant
    - a PR interval >250 ms
    - a QRS interval >130 ms
    - a QTcF interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where QTcF = QT/RR0.33)
    - A patient should also be excluded if he or she has any other abnormal ECG tests that in the investigator's clinical judgment are medically significant and would impact the safety of the patient or the interpretation of the study results.

For patients who completed the dosing period of study 16323A

General

1. The patient has previously been enrolled in this study.
2. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
3. The patient has developed a severe drug allergy or hypersensitivity to the IMP or its excipients during study 16323A.
4. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

Psychiatric

5. The patient has been diagnosed with a primary psychiatric disorder other than schizophrenia during study 16323A.
6. The patient has a clinically significant unstable illness diagnosed during study 16323A.
7. The patient is experiencing an acute exacerbation of his/her psychotic symptoms according to the investigator's clinical judgement.
8. The patient has a current diagnosis of substance use disorder according to DSM 5™ criteria during study 16323A with the exception of tobacco, or mild cannabis or mild alcohol use disorder. Patients with a positive drug screen test at the Baseline Visit, with the exception of cannabis and verified by repeated testing, are excluded from the study.
9. The patient, in the opinion of the investigator, is at significant risk of suicide, or the patient:
    - Answers "Yes" to any question on the Suicidal Behaviour section of the C-SSRS, OR
    - Answers "Yes" to questions 4 and 5 on the Suicidal Ideation section of the C-SSRS.

10. The patient has started formal cognitive or behavioural therapy or systematic psychotherapy during study 16323A. Any ongoing formal psychotherapy initiated more than 6 weeks prior to Screening Visit of study 16323A should be continued with the same methodology and at the same frequency and intensity during the entire study.
11. The patient has experienced neuroleptic malignant syndrome during study 16323A.

Medical

12. The patient has any other medical disease for which the treatment takes priority over treatment of schizophrenia or is likely to interfere with study treatment or impair treatment compliance.
13. The patient has a moderate or severe ongoing adverse event related to IMP from study 16323A considered of potential safety risk by the investigator.
14. The patient takes or has taken disallowed recent or concomitant medication (specified in Appendix II) in study 16323A.
15. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability or efficacy, or interfere with the conduct or interpretation of the study.
16. The patient has clinically significant abnormal vital signs considered of potential safety risk by the investigator.
17. The patient has one or more laboratory values outside the reference range, based on the last available blood or urine samples taken during study 16323A that are, in the investigator's opinion, of potential risk to the patient's safety, or the patient has any of the following values at study 16323A (the medical monitor should be contacted in case of uncertainty):
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
18. The patient has not previously been diagnosed with diabetes, but meets ANY of the following criteria (newly diagnosed diabetes) based on the last available blood samples taken during study 16323A:
    - HbA1c ≥7.0%, OR
    - glucose >6.94 mmol/L (fasting, >125 mg/dL) or >11.1 mmol/L (nonfasting, >200 mg/dL)
    - any other abnormal laboratory tests that in the investigator's clinical judgement are medically significant and would impact on the safety of the patient or the interpretation of the study results.
19. The patient has orthostatic hypotension (defined as a decrease in systolic blood pressure >20 mmHg between two measurements, first in the supine position and then sitting, and standing after the patient has rested in each position for at least 3 minutes.
20. The patient has, based on the last available ECG measurement taken during study 16323A:
    - an abnormal ECG that is, in the investigator's opinion, clinically significant

- a PR interval >250 ms
- a QRS interval >130 ms
- a QTcF interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where QTcF = QT/RR0.33)
- A patient should also be excluded if he or she has any other abnormal ECG tests that in the investigator's judgment are medically significant and would impact the safety of the patient or the interpretation of the study results.

For patients who can potentially benefit from treatment with Lu AF35700

General

1. The patient has previously been enrolled in this study.
2. The patient has participated in a clinical study <30 days prior to the Screening Visit.
3. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
4. The patient is under forced treatment.
5. The patient is pregnant or breast-feeding.
6. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity to any of the IMP(s) or its/their excipients.
7. The patient has a disease or takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.
8. The patient takes or has taken disallowed recent or concomitant medication (specified in Appendix II) or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study.
9. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

Psychiatric

10. The patient has any current psychiatric disorder (DSM-5™ criteria) other than schizophrenia established as the primary diagnosis.
11. The patient suffers from intellectual disability, organic mental disorders, or mental disorders due to a general medical condition (DSM-5™ criteria).
12. The patient is experiencing acute exacerbation of his/her psychotic symptoms at the Screening Visit, between the Screening and Baseline Visits or at the Baseline Visit according to the investigator's judgment.
13. The patient is treated with clozapine at the time of the Screening Visit.
14. The patient has a current diagnosis or a history of substance use disorder according to DSM-5™ criteria within 6 months prior to the Screening Visit with the exception of tobacco, or mild cannabis or mild alcohol use disorder. Patients with a positive drug screen test with the exception of cannabis and verified by repeated testing are excluded from the study.

15. The patient is at significant risk of harming himself/herself or others according to the investigator's clinical judgement, or who on the C-SSRS:
    - Answers "Yes" to questions 4 or 5 on the Suicidal Ideation section within the last 3 months at Screening, OR
    - Answers "Yes" to any question on the Suicidal Behaviour section within the last 3 months at Screening, OR
    - Answers "Yes" to questions 4 or 5 on the on the Suicidal Ideation section at Baseline.
16. The patient has had neuroleptic malignant syndrome.
17. The patient has started formal cognitive or behavioural therapy or systematic psychotherapy within 6 weeks prior to Screening, or plans to start such therapy during the study. Any ongoing formal psychotherapy initiated more than 6 weeks prior to Screening should be continued with the same methodology and at the same frequency and intensity during the entire study.

Medical

18. The patient has any other medical disease for which the treatment takes priority over treatment of schizophrenia or is likely to interfere with study treatment or impair treatment compliance.
19. The patient has a history of moderate or severe head trauma or other neurological disorders or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning.
20. The patient has epilepsy or a history of seizures, except for a single seizure episode (e.g., childhood febrile seizure, post traumatic, or alcohol withdrawal).
21. The patient has or has had one or more of the following conditions that is/are considered clinically relevant in the context of the study:
    - neurological disorder
    - cardiovascular disease
    - seizure disorder or encephalopathy
    - congestive heart failure
    - cardiac hypertrophy
    - arrhythmia
    - bradycardia (pulse <50 bpm)
    - respiratory disease
    - hepatic impairment or renal insufficiency
    - metabolic disorder
    - endocrine disorder
    - gastrointestinal disorder
    - haematological disorder
    - infectious disorder
    - any clinically significant immunological condition
    - dermatological disorder

- venereal disease
- elevated intra-ocular pressure or is at risk of acute narrow-angle glaucoma

22. The patient has clinically significant abnormal vital signs.
23. The patient has one or more clinical laboratory test values outside the reference range, based on the blood and urine samples taken at the Screening Visit, that are of potential risk to the patient's safety, or the patient has, at the Screening Visit:
    - a serum creatinine value >1.5 times the upper limit of the reference range
    - a serum total bilirubin value >1.5 times the upper limit of the reference range
    - a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 times the upper limit of the reference range
24. The patient has not previously been diagnosed with diabetes, but meets ANY of the following criteria (newly diagnosed diabetes):
    - HbA1C >6.5%, OR
    - Fasting plasma glucose >126 mg/dL (7.0 mmol/L), OR
    - Non-fasting plasma glucose >200 mg/dL (11.1 mmol).
25. The patient has previously been diagnosed with diabetes, but the condition is unstable as determined by ANY of the following criteria:
    - HbA1c ≥7.0%, OR
    - Screening glucose is >6.94 mmol/L (fasting, >125 mg/dL) or 11.1 mmol/L (nonfasting, 200 mg/dL). If the non-fasting screening glucose is 11.1 mmol/L (200 mg/dL), patients must be retested in a fasted state and the retest value must be ≤6.94 mmol/L (125 mg/dL) to be eligible for the study, OR
    - The patient has not been maintained on a stable regimen of insulin and/or oral antidiabetic medication(s) for at least 28 days prior to Screening or the diabetes has not been well-controlled by diet for at least 28 days prior to Screening, OR
    - The patient has been hospitalized within 6 months prior to Screening due to diabetes or complications related to diabetes
26. The patient has orthostatic hypotension (defined as a decrease in systolic blood pressure >20 mmHg between two measurements, first in the supine position and then sitting, and standing after the patient has rested in each position for at least 3 minutes.
27. The patient has, at the Screening or at the Baseline Visit:
    - an abnormal ECG that is, in the investigator's opinion, clinically significant
    - a PR interval >250 ms
    - a QRS interval >130 ms
    - a QTcF interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where QTcF = QT/RR0.33)
    - A patient should also be excluded if he or she has any other abnormal ECG tests that in the investigator's judgment are medically significant and would impact the safety of the patient or the interpretation of the study results.
28. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin, that has not been in remission for >5 years prior to the first dose of IMP.

5.4 Withdrawal Criteria

A patient must be withdrawn from the study if:

- the patient and/or his or her legal representative (if applicable) withdraw(s) his or her consent (defined as a patient and/or his or her legal representative [if applicable] who explicitly take(s) back his or her consent); section 8.4 states how the patient's data will be handled
- the patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient via both phone and mail]).

A patient must be withdrawn from treatment if:

- the investigator considers it, for safety, lack of efficacy, and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn
- the patient becomes pregnant
- the patient has a serum ALT or AST value >3 times the upper limit of the reference range and a serum total bilirubin value >2 times the upper limit of the reference range
- the patient has a serum ALT or AST value >5 times the upper limit of the reference range that is confirmed by testing <2 weeks later
- the patient has a QTcF interval >500 ms or a change from Screening (or from Baseline for *16159A-patients* and *16323A-patients*) in the QTcF interval >60 ms concurrently with a QTcF interval >470 ms
- the patient has a positive urine drug screen verified by repeated testing at the following site visit
- the patient fails to comply with study procedures
- the patient is <80% IMP compliant between two consecutive, scheduled visits
- the patient in the opinion of the investigator has significant risk of suicide or who answers "Yes" to suicidal ideation questions 4 or 5 or answers "Yes" to suicidal behaviour on the C-SSRS® at any time during the study

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products

6.1 Treatment Regimen

A schematic representation of the Treatment Regimen is presented in Panel 3 below. The total treatment period is 52 weeks.

For patients who completed study 16159A (*16159A-patients*)

The Baseline Visit will take place at the same visit as the Visit 12 (Primary Outcome Visit, end of Week 16) of the study 16159A.

After the baseline assessment, for eligible patients, the treatment with Lu AF35700 will be initiated at daily dose of 10 mg at Day 1 of study 16159B. In addition, for *16159A-patients*, the treatment (Lu AF35700, risperidone or olanzapine) received during study 16159A will be tapered down in a blinded fashion with wallets from study 16159A and will be completed in 7 days according to the following scheme:

- Patients randomised to Risperidone: 4 mg/day for the first 3 days; 2 mg/day for the 4 subsequent days, encapsulated tablets, orally, once daily
- Patients randomised to Olanzapine: 10 mg/day for the first 3 days; 5 mg/day for the 4 subsequent days, encapsulated tablets, orally, once daily
- Patients randomised to Lu AF35700: Placebo for 7 days, encapsulated tablets, orally, once daily.

At the end of the first week (Week 1 Visit), all patients will be treated with 10 mg/day Lu AF35700 only.

From the Week 1 Visit, according to the investigator's clinical judgment, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment. This can occur at scheduled or unscheduled visits.

From the Week 8 Visit, the switch from Lu AF35700 daily dosing regimen to Lu AF35700 weekly dosing regimen can be performed at any consecutive visit according to the investigator's clinical judgment. The first weekly tablet will be taken 7 days after the last daily tablet. The Lu AF35700 weekly dosing regimen can be switched back to a daily dosing regimen of 10 mg/day for tolerability reasons or to 20 mg/day for worsening of the patient's clinical status. This can occur at scheduled or unscheduled visits. The first daily tablet will be taken 7 days after the last weekly tablet.

The number of patients under weekly dosing regimen will be limited to 50 patients by IVRS/IWRS.

For patients who completed the dosing period of the study 16323A (*16323A-patients*)

The Baseline Visit of study 16159B will take place at the same visit as the last day of the dosing period of study 16323A.

After the baseline assessment, for eligible patients, the treatment with Lu AF35700 will be initiated at daily dose of 10 mg at Day 1 of study 16159B. In addition, for *16323A-patients*, the treatment (Lu AF35700 or quetiapine) received during study 16323A will be tapered down in a blinded fashion and will be completed in 7 days according to the following scheme:

- Patients randomised to quetiapine: 600 mg/day for the first 3 days; 300 mg/day for the 4 subsequent days, encapsulated tablets, orally, once daily.
- Patients randomised to Lu AF35700: Placebo for 7 days, encapsulated tablets, orally, once daily.

At the end of the first week (Week 1 Visit), all patients will be treated with 10 mg/day Lu AF35700 only.

At visits following the Week 1 Visit, according to the investigator's clinical judgment, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment. This can occur at scheduled or unscheduled visits.

For other patients who can potentially benefit from treatment with Lu AF35700 (*Other Patients*)

After the baseline assessment, for eligible patients, the current antipsychotic treatment will be tapered down and completed in 7 days, while the treatment with Lu AF35700 will be initiated at a 10 mg/day dose at Day 1. The 10 mg/day dose will be maintained during the first week of study 16159B.

At the end of the first week (Week 1 Visit), all patients will be treated with 10 mg/day Lu AF35700 only.

At visits following the Week 1 Visit, according to the investigator's clinical judgment, the 10 mg/day dose can be increased to 20 mg/day based on the patient's response. Thereafter, the 20 mg/day dose can be reduced to 10 mg/day based on the patient's tolerability to treatment. This can occur at scheduled or unscheduled visits.

The recruitment of *Other Patients* can start in a given site only after the recruitment of the patients in the study 16159A or in the study 16323A is completed.

Panel 3 Treatment regimen

Patients who completed study 16159A				**Patients who completed study 16323A**		**Other Patients**
Investigational Medicinal Product (IMP)	*Lu AF35700 10 or 20 mg/day Encapsulated tablets*	*OLZ 15-20 mg/day Encapsulated tablets*	*RIS 4-6 mg/day Encapsulated tablets*	*Lu AF35700 10 & 30 mg/day Encapsulated tablets*	*Quetiapine 800 mg/day Encapsulated tablets*	*N/A*
Treatment that will be taken in study 16159B						
Day 1 – Day 3 *Down-titration wallet from the previous study* Wallet from study 16159B	*Placebo Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*OLZ 10 mg/day Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*RIS 4 mg/day Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*Placebo Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*QUE 600 mg/day Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*N/A* Lu AF35700 10 mg/day, tablets + Current antipsychotic treatment will be gradually down-titrated and completed in 7 days (based on the SmPC or equivalent document/label)
Day 4 – Day 7 *Down titration wallet from the previous study* Wallet from study 16159B	*Placebo Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*OLZ 5 mg/day Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*RIS 2 mg/day Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*Placebo Encapsulated tablets* Lu AF35700 10 mg/day, tablets	*QUE 300 mg/day Encapsulated tablets* Lu AF35700 10 mg/day, tablets	
Day 8 – Day 55	Lu AF35700 10 or 20 mg/day, tablets	Lu AF35700 10 or 20 mg/day, tablets	Lu AF35700 10 or 20 mg/day, tablets	Lu AF35700 10 or 20 mg/day, tablets	Lu AF35700 10 or 20 mg/day, tablets	Lu AF35700 10 or 20 mg/day, tablets
From Day 56	Lu AF35700 10 or 20 mg/day, tablet Lu AF35700 70 mg/week, tablets - The switch from Lu AF35700 daily dosing regimen (10 or 20 mg/day) to Lu AF35700 weekly dosing regimen can be performed at the end of the eighth week (Week 8 Visit), according to the investigator's clinical judgment). First weekly tablet will be taken 7 days after the last daily tablet. - No more than 50 patients can be assigned to weekly dosing regimen during the course of the study. - Possibility to switch back to daily dosing regimen (for lack of tolerability or symptoms worsening). First daily tablet will be taken 7 days after the last weekly tablet.			Lu AF35700 10 or 20 mg/day, tablets		

6.2 IMPs, Formulations, and Strengths

The IMPs supplied by Lundbeck in this study are:

- Lu AF35700 – film-coated tablets in strengths of 10 and 20 mg (once daily) and 70 mg (once weekly)

6.3 Manufacturing, Packaging, Labelling, and Storage of IMPs

The IMPs will be manufactured, packaged, labelled, released (by a qualified person [QP]), and distributed in accordance with the principles of *Good Manufacturing Practice*, under the responsibility of Lundbeck.

The IMP will be provided in wallet cards.

The wording on the labels will be in accordance with *Good Manufacturing Practice* regarding labelling and national and/or local regulatory requirements. If additional information is to be added when the IMP is dispensed to patients, this will be clearly stated on the labels, and the investigator will be instructed to do so.

No manipulation, repackaging, or relabelling of IMP is permitted after QP release by Lundbeck, unless a repackaging/relabelling agreement exists, and the documentation is available to the Department of Clinical Supply, H. Lundbeck A/S, and, where necessary, new QP releases are made.

The IMPs will be identified using a unique IMP number.

The IMPs must be stored in a safe and secure location, and in accordance with the storage conditions specified on the labels.

6.4 Method of Assigning Patients to Treatment

All patients will be assigned a screening number by eCRF system and that will be used to identify them throughout the study.

An interactive voice response system (IVRS) will be used in this study. The IVRS will dispense Lu AF35700 daily dosing (10 or 20 mg), and provide the option to the investigator to switch to weekly dosing regime at the end of the eighth week. The IVRS will restrict the number of patients that can be assigned to weekly dosing to 50 patients. The IVRS will allow the patient to be switched back from weekly to daily dosing.

6.5 IMP Accountability

The IMPs must be tracked at each site using two logs:

- a site-specific log to track the complete inventory (that is, what is shipped between the site and the depot)
- a patient-specific log to track what is dispensed to and returned by the patient

The investigator and the pharmacist (if applicable) must agree to only dispense IMP to patients enrolled in the study. The investigator or the pharmacist (if applicable) must maintain an adequate record of the receipt and distribution of the IMPs. This record must be available for inspection at any time.

6.6 Post -study Access to IMP

Post-study access to IMP will not be available. Patients in the study will have access to appropriate medical care after they complete or withdraw from the study.

7 Concomitant Medication

Concomitant medication is any medication other than the IMPs that are taken during the study, including during the Screening Period.

The recent and concomitant medications that are disallowed or allowed with restrictions during the study are summarised in Appendix II.

Details of all concomitant medication (prescription and over-the-counter) taken at the last visit of studies 16159A, and 16623A and taken <3 months prior to the Screening Visit for patients in need of a change in antipsychotic treatment must be recorded in the eCRF at the first visit. Any changes (including reason for changes) in concomitant medication must be recorded at each subsequent visit. For any concomitant medication initiated or for which the dose has changed due to a new disorder or worsening of a concurrent disorder, the disorder must be recorded as an adverse event. Concomitant medication, associated with adverse events and SAEs, initiated after the last dose of IMP, must be recorded.

8 Study Visit Plan

8.1 Overview

An overview of the procedures and assessments to be conducted during the study and their timing is presented in Panel 2. Further details are in chapter 9.

After completing or withdrawing from the study, the patient must be treated in accordance with usual clinical practice.

8.2 Screening Visit (Visit 1)

Only patients who did not previously participate in a study investigating Lu AF35700 will enter this study at the screening visit.

The screening period begins after the informed consent has been obtained. Washout of disallowed medications begins, if applicable, and must comply with the requirements listed in Appendix II. Screening evaluations are described in Panel 2.

In exceptional cases, the visit interval between the Screening and Baseline Visit may be extended with consent from the Sponsor Medical Expert, provided the Medical Expert accepts the rationale provided for the extension.

The patient's eligibility assessment will be reviewed by an external medical team based on key protocol inclusion and exclusion criteria to promote appropriate patient enrolment and data quality. Sites should submit specific screening information within 48 hours from the Screening Visit. Once all information is obtained, the external medical team confirm the site whether the patient can continue screening.

Decisions regarding inclusion of patients and assessment of patient safety throughout the study primarily remain at the discretion of the investigator; however, the sponsor or external medical team may request exclusion or discontinuation of a patient based on entry criteria or patient safety.

8.2.1 Pre-screening

Only for *Other Patients* - Each site must record in a pre-screening log which patients attended the Screening Visit

8.2.2 Patient Identification Card

Each patient will be provided with a patient identification card that states, at a minimum, the name of the IMP, the study number, the patient identification number, the investigator's name, and an emergency telephone number providing 24-hour service.

The patient identification card should be returned to the investigator upon completion of the patient's participation in the study.

8.2.3 Re-screening

Re-screening is not allowed in this study.

8.3 Baseline Visit (Visit 2)

Patients previously participating in a study investigating Lu AF35700 will enter in this study directly at the baseline visit. The investigator's evaluation of the patient's eligibility in this study will be done based on the latest data available in the previous LuAF35700 study.

After the baseline visit, the current antipsychotic or study treatment will be tapered down and completed in 7 days.

8.4 Withdrawal Visit

Patients who withdraw from the study prior to the Primary Outcome Visit will be asked to attend a Withdrawal Visit, if at all possible. The visit must be scheduled as soon as possible after withdrawal.

No new information will be collected from patients who withdraw, except information collected in relation to the scheduled Withdrawal Visit or needed for the follow-up of adverse events (section 10.5).

The reason for withdrawal must be recorded on the *Reason for Withdrawal Form*.

For a patient and his or her legal representative (if applicable) who withdraw(s) consent:

- if the patient and his or her legal representative (if applicable) withdraw(s) consent during a visit and then agrees to it being the final visit, the investigator will complete the visit as a Withdrawal Visit and all the data collected up to and including this visit will be used.
- if the patient and his or her legal representative (if applicable) withdraw(s) consent during a telephone conversation, the investigator will ask the patient if he or she will attend a Withdrawal Visit. If the patient:
  - agrees to attend a Withdrawal Visit, all the data collected up to and including this visit will be used.
  - refuses to attend a Withdrawal Visit, the investigator should attempt to follow the patient's safety and future treatment; any information collected will only be recorded in the patient's medical record.
- if the patient and his or her legal representative (if applicable) explicitly request(s) that his or her data collected from the time of withdrawal of consent onwards not be used, this will be respected.

8.5 Safety Follow-up Visit/Contact (Visit 18)

The safety follow-up is conducted to capture serious adverse events (SAEs) that occur during the Safety Follow-up Period as well as to follow up on the outcome of adverse events ongoing at the end of the Treatment Period. The safety follow-up must be conducted 42 days (+3 days) after the last dose of IMP. The safety follow-up may either be conducted as a visit to the site or as a telephone contact.

If any new SAEs have occurred since the last assessment at which the patient received IMP, the safety follow-up must, when possible, be a visit to the site.

For adverse events that were ongoing at the end of the Treatment Period and that resolved during the Safety Follow-up Period, the stop date must be recorded. For non-serious adverse events still ongoing at the safety follow-up, the stop date must be recorded as "ongoing". SAEs must be followed until resolution or the outcome is known.

Patients with a clinical safety laboratory test value that was out-of-range at the Primary Outcome or Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 42 days or until the value normalises or stabilises or a diagnosis or a reasonable explanation has been established. For these patients, safety follow-up visits must be scheduled to allow for a medical examination and/or blood sampling. The investigator must decide whether further safety follow-up visits are required after 42 days. If further safety follow-up visits are made, these must be documented in the patient's medical record and not in the eCRF.

Patients who withdrew due to elevated AST or ALT values (see section 5.4) should be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established (see section 10.5).

The safety follow-up for patients who withdraw consent must be performed, if at all possible; any information collected will be recorded in the patients' medical records.

8.6 End-of-study Definition

The end of the study for an individual patient is defined as the last protocol-specified contact with that patient. The overall end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study.

9 Assessments

9.1 Screening and Baseline Procedures and Assessments

9.1.1 Demographics and Other Baseline Characteristics

For *Other Patients* - At the Screening Visit, the following will be recorded or assessed:

- Diagnosis (DSM-5^{TM})
- Relevant medical and psychiatric history
- Previous medications taken within (minimum) 3 months of screening; previous standard of care oral antipsychotic drugs taken within 3 months of screening. Washout from any prohibited concomitant medications will begin, if applicable (see Appendix II)
- Demographics: age, sex, race
- Height, weight, waist circumference
- Social history (e.g. education level, marital status, current living status, current employment status)

Prior to enrolling a patient in the study, the investigator must ascertain that the patient meets the selection criteria.

9.1.2 Drug Screen

A urine drug screen for opiates, methadone, cocaine, amphetamines (including ecstasy/methamphetamine), barbiturates, benzodiazepines, phencyclidine, and cannabinoids will be performed at designated times, but can be performed at any time during the study at the discretion of the investigator.

The urine drug screening kit will be supplied by a central laboratory.

9.2 Effectiveness Assessments

9.2.1 Clinician-rated scales

9.2.1.1 Use of clinician-rated scales

The following clinician-rated scales will be used as exploratory effectiveness assessments:

- PANSS − assessing symptoms of schizophrenia
- PSP − assessing personal and social performance
- CGI-S − assessing global impression
- NSA-4 – assessing the severity of negative symptoms of schizophrenia
- QLS – assessing quality of life
- WoRQ – assessing readiness to work in patients with schizophrenia

The PANSS, NSA-4 and QLS will be administered in the local language. The PSP, CGI-S and WorQ will be administered in English only. Only scales provided by Lundbeck designated provider that, have been validated in the language to which they have been translated, will be used in this study.

Detailed instructions on how to administer the scales and how to score using the scales will be provided to the site.

9.2.1.2 Positive and Negative Syndrome Scale (PANSS)

The PANSS[11] is a clinician-rated scale designed to measure severity of psychopathology in adult patients with schizophrenia, schizoaffective disorders, and other psychotic disorders. It emphasises positive and negative symptoms. The PANSS comprises 3 sub-scales with a total of 30 items: 7 items constitute the Positive Symptoms subscale (for example: delusions, conceptual disorganization, and hallucinatory behaviour), 7 items constitute the Negative Symptoms subscale (for example: blunted affect, emotional withdrawal, and poor rapport), and 16 items constitute the General Psychopathology subscale (for example: somatic concern, anxiety, and guilt feelings). Each item is rated from 1 (symptom not present) to 7 (symptom extremely severe). Raters using the PANSS should have training in psychiatric interview techniques and have clinical experience working with patients with schizophrenia and related psychotic disorders. The Structured Clinical Interview for PANSS[21] (SCI–PANSS) will be used to facilitate the administration of the PANSS assessment.

It takes 30 to 40 minutes to administer and score the PANSS.

9.2.1.3 Personal and Social Performance Scale (PSP)

The PSP[14] is a clinician-rated scale designed and validated to measure a patient'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 are assessed on a 6-point scale, from absent to very severe. Based on these assessments and their combination, the global score ranges from 1 to 100.

The PSP can be administered by an experienced clinician after a short training session.

It takes approximately 5 minutes to administer and score the PSP.

9.2.1.4 Clinical Global Impression Scale- Severity (CGI-S)

The CGI[12] was developed to provide global measures of the severity of a patient's clinical condition during clinical studies. The CGI severity of illness (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). An experienced clinician can use the CGI after a short training session.

It takes 1 to 2 minutes to score the CGI after a clinical interview.

9.2.1.5 4-Item Negative Symptom Assessment (NSA-4)

The NSA-4[13] is a clinician rated scale designed to assess the severity of negative symptoms of schizophrenia. It consists of 4 items to measure: restricted speech quantity, reduced emotion, reduced social drive, and reduced interests, as well as an overall global rating of negative symptoms. Each of the four items is rated on a 1 to 6-point scale where '1' represents no reduction from normal behaviors associated with the item and '6' represents severe reduction or absence of the behavior. The scale also includes a "non ratable" designation denoted as '9'.

It takes approximately 10 minutes to complete the NSA-4.

9.2.1.6 Quality of Life Scale (QLS)

The QLS[15] is a clinician-rated scale designed to assess deficit symptoms of schizophrenia and functioning during the preceding 4 weeks. The QLS consists of 21 items in 4 subscales: Interpersonal Relations (8 items), Instrumental Role (4 items), Intrapsychic Foundations (7 items), and Common Objects and Activities (2 items). Each item is rated on a 7-point scale, from 0 (severe impairment) to 6 (normal or unimpaired functioning). Definitions are provided for 4 anchor points of the 7 points. Each item has a brief description of the judgement to be made and a set of suggested probes for the clinician. The mean score is calculated for each subscale and the total score for all items ranges from 0 to 126, where the higher score indicates normal or unimpaired functioning. The QLS can be administered by a clinician after a short training.

It takes approximately 45 minutes to administer and score the QLS.

9.2.1.7 Readiness for work questionnaire (WoRQ)

The WoRQ[16] is a clinician-rated scale designed to measure readiness to work in patients with schizophrenia. The WoRQ consists of 8 items: the clinician must rate 7 statements and answer one question. The statements are rated on a 4-point scale, from *strongly agree, agree, disagree* or *strongly disagree* based on all material available (for example, personal notes, medical records, input from other health professionals, family members or caregivers); and in the final item, the clinician must indicate if the patient is ready for work or not. The WoRQ can be rated by a clinician after a short training session.

It takes approximately 5 minutes to administer the WoRQ.

9.2.1.8 Rater Qualification and Certification

The PANSS, PSP, NSA-4, QLS, and WoRQ should be administrated by clinicians.

The CGI-S must be administered by the clinician responsible for the patient.

A clinician in the context of the study is defined as a Medical Doctor (MD), Doctor of Osteopathic Medicine (DO), or anyone holding a Doctoral or Master's Degree (or equivalent) in a medical or psychology related field.

As a pre-requisite, PANSS raters must be experienced in patients with schizophrenia and in administering the PANSS.

Any exceptions must be discussed and approved by Lundbeck.

Only raters who have been already trained and certified in studies 16159A and 16323A are allowed to rate the patients in study 16159B. New raters joining study 16159B will be trained and certified using the same certification processes as in study 16159A.

Documentation of training and certification will be delivered to the raters for archiving in the investigator study master file (TMF). No patient may be rated before the documentation has been delivered.

Rater training and certification will be conducted by a third party vendor selected by the sponsor.

Each site should have a minimum of 2 certified raters per scale in order to provide back-up for each other. Any exceptions must be discussed and approved by Lundbeck.

9.2.2 Patient Reported Outcomes (PROs)

9.2.2.1 Use of patient reported outcomes

The following PROs will be used:

- MSQ – patient reported, assessing satisfaction with medication
- TooL – patient reported, assessing impacts of side effects on quality of life

Only scales provided by H. Lundbeck A/S and that have been validated in the language to which they have been translated will be used in this study. The MSQ and TooL will be completed by the patient in the local language and guidance will be given to the patients on how to complete it/them.

Detailed instructions on how to administer the scales will be provided to the site.

9.2.2.2 Medication Satisfaction Questionnaire (MSQ)

The MSQ[17] is a patient-rated scale designed and validated to assess the patient's satisfaction with his or her current antipsychotic medication. The MSQ consists of one item that is rated on a 7-point scale ranging from 1 (extremely dissatisfied) to 7 (extremely satisfied). The patient can complete the MSQ without any training.

It takes less than 1 minute to complete the MSQ.

9.2.2.3 Tolerability and Quality of Life questionnaire (TooL)

The TooL[18] is a patient-rated scale developed to measure the impact of side-effects on the quality of life in patients treated with antipsychotic medication. The TooL consists of eight domains: mood (worry-upset), function capabilities, fatigue-weakness, weight gain, stiffness-tremor, physical restlessness, sexual dysfunction and dizziness-nausea. Each domain is rated on a 4-point scale from 1 (no impact) to 4 (maximum impact). Total scores range from 8 (no impact) to 32 (maximum impact).

It takes approximately 5 minutes to complete the TooL.

9.2.3 Health Care Resource Utilisation

The Health Economic Assessment (HEA) questionnaire will be used to collect resource utilisation. The HEA will be provided in English only. Country specific version will be used for US and Canada. Instructions on how to complete the scale will be provided to the site.

The HEA is a questionnaire aiming at monitoring patients' health care resource utilisation such as physicians' visits, outpatient and inpatient services and other relevant services. Site personnel involved in the conduct of the study must ask these questions to the patients at selected visits. This allows for relating cost data to clinical efficacy and safety, and these data may be used for cost-effectiveness analyses.

The HEA is available in a Baseline Evaluation version which is to be used at the Baseline Visit and a Follow-Up Evaluation version which is to be used at Primary Outcome/ Withdrawal Visit.

It takes approximately 15 minutes to complete the HEA.

9.3 Pharmacokinetic Assessments

Blood samples for IMP quantification (2 mL per time point) will be drawn in 2 mL K3 EDTA tube in accordance with Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

Sampling time point and sampling date should be recorded. At the visits for PK assessments, the time point and date of the latest intake of study medication should be recorded and the patient should be asked about the usual time of study medication intake during the period since the last visit.

The blood samples will be analysed for Lu AF35700 and Lu AF36152 using an analytical method validated in accordance with the EMA *Guideline on Bioanalytical Method Validation*[22] and the FDA *Guidance for Industry*.[23]

If other metabolites are identified and considered significant, these may be included in an exploratory analysis. The bioanalysis will be performed by the Department of Bioanalysis, H. Lundbeck A/S. A bioanalytical protocol will be prepared by Lundbeck before the plasma samples are analysed.

The result of the analysis will not be reported back to the investigator.

9.4 Translational Medicines Assessments (For *Other Patients* only)

9.4.1 General Considerations

Although the possible future exploratory biomarker analyses will help to increase our understanding of the aetiology of schizophrenia and the molecular basis of the drug response, the efforts described in this protocol are strictly research based. Therefore, as the complex interactions between genes and disease are currently not characterised to a level that translates to a meaningful clinical advantage, individual results from the exploratory biomarker analyses will not be given to the patients. For the same reasons, individual results will not be added to the patients' medical records.

The patients will have no direct benefit from the exploratory biomarker analyses. As blood sampling for the exploratory genomics, proteomics, and metabolomics is an integral part of the study, the main *Patient Information Sheet* covers these analyses. Conversely, blood sampling for the possible future genetic biomarker analysis is optional and a separate Patient Information Sheet covers this analysis.

The blood samples for biobanking and possible future exploratory biomarker analysis, or the data derived from these blood samples, may be shared with academic and public institutions and other companies. However, Lundbeck will retain full control of the samples and their use in accordance with the information in the *Patient Information Sheet* and a Material Transfer

Agreement. Furthermore, the results based on the analysis of the samples may be pooled across studies to increase the statistical power of the analyses.

A patient and/or his or her legal representative (if applicable) may, at any time and without stating a reason, specifically request the destruction of the patient's exploratory biomarker sample, irrespective of his or her continued participation in the study. The investigator must send a written request on behalf of the patient to the international study manager. The investigator will receive written confirmation from Lundbeck when the sample has been destroyed.

The blood samples for genomics, proteomics, and metabolomics will be single-coded using the patient's screening number. The blood samples for genetic biomarker analysis will be double-coded as described in EMA's position paper on pharmacogenetic terminology[24] to ensure patient privacy protection.

The results of the possible future pharmacogenetics, proteomics/metabolomics and gene expression profiling will not be reported to the investigator.

9.4.2 Blood Sampling for Gene Expression Profiling

Blood samples for gene expression profiling (RNA) will be collected in two PAXgene tubes (2,5 mL) at each time point. The maximum volume of blood to be collected during the study for this purpose will be 10 mL. Samples for gene expression profiling will be shipped to a Central Laboratory, United States, for sample storage and possible preparation and analysis.

The result of the analysis will not be reported back to the investigator.

Only the patients not previously participating in a study investigating Lu AF35700 will have blood drawn for gene expression profiling.

9.4.3 Blood Sampling for Metabolomic/Proteomic Biomarkers

Blood samples for metabolomic/proteomic biomarkers will be collected in one 10 mL K2 EDTA tube at each time point. The maximum volume of blood to be collected during the study for this purpose will be 20 mL. The samples for metabolomic/proteomic biomarkers will be shipped to a Central Laboratory, United States, for sample storage.

Only the patients not previously participating in a study investigating Lu AF35700 will have blood drawn for metabolomics/proteomic biomarkers.

9.4.4 Blood Sampling for Pharmacogenetics

It is optional for the patient to donate a blood sample for exploratory pharmacogenetic analysis. A blood sample (9 mL) will be collected in K3 EDTA tubes for subsequent DNA extraction. Blood tubes will be shipped on dry ice to a Central Laboratory, United States, where DNA will be extracted and retained. DNA aliquots will be shipped to a Central

Laboratory, for storage. The genetic variants to be analysed may include single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). The analytical methods may be polymerase chain reaction (PCR), qPCR (quantitative PCR), sequencing, or whole genome scans on microarrays.

The results of these analyses are not specifically related to this study. The sample will be stored at a Central Laboratory, United States.

Only patients not previously participating in a study investigating Lu AF35700 will have blood drawn for pharmacogenetic analysis.

9.5 Safety Assessments

9.5.1 Adverse Events

The patients will be asked a non-leading question (for example, “how do you feel?”, “how have you felt since your last visit?”) at each visit, starting at the Screening Visit. Adverse events (including worsening of concurrent disorders, new disorders, and pregnancies) either observed by the investigator or reported spontaneously by the patient will be recorded, and the investigator will assess the seriousness and the intensity of the adverse event and its relationship to the IMP. Results from relevant tests and examinations, such as clinical safety laboratory tests, vital signs, and ECGs, or their corresponding conditions will also be recorded as adverse events if considered by the investigator to be clinically significant.

See chapter 10 for further information on adverse events.

9.5.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 4.

Panel 4 Clinical Safety Laboratory Tests

Haematology	**Liver**[a]	**Kidney**[a]
B-haemoglobin	S-total bilirubin	S-creatinine
B-erythrocyte count	S-conjugated bilirubin	S-urea nitrogen (BUN)
B-haematocrit	S-alkaline phosphatase (AP)	S-uric acid
B-MCV	S-alanine aminotransferase (ALT)	**Urine (dipstick)**
B-MCHC	S-aspartate aminotransferase (AST)	U-protein (dipstick)
B-total leucocyte count	S-lactate dehydrogenase (LDH)	U-glucose (dipstick)
B-neutrophils (% of total leucocytes)	S-γ-glutamyl transferase (γGT)	U-blood (dipstick)
B-eosinophils (% of total leucocytes)	**Electrolytes**[a]	U-ketones (dipstick)
B-basophils (% of total leucocytes)	S-sodium	**Urine drug screen**[c]
B-lymphocytes (% of total leucocytes)	S-potassium	U-Amphetamine
B-monocytes (% of total leucocytes)	S-chloride	U-Barbiturates
B-thrombocyte count	S-bicarbonate	U-Benzodiazepines
P-INR (prothrombin ratio)	S-calcium (total)	U-Cannabinoids
Lipids[a]	**Endocrine and Metabolic**[a]	U-Cocaine
S-cholesterol (total) (fasting)	S-albumin	U-Methadone
S-triglycerides (fasting)	P-glucose (fasting)	U-Opiates
S-low density lipoprotein (LDL)	S-prolactin[b]	U-Phencyclidine
S-high density lipoprotein (HDL)	B-HbA1c (fasting)	**Pregnancy (women only)**
	S-total protein	S-hCG
		Urine dipstick[d]
		Additional Test
		S-Creatine phosphokinase (CPK)[e]
B – blood; P – plasma; S – serum; U – urine		

a. Clinical chemistry
b. Result will remain blinded
c. Urine samples will be collected and analysed at the site using dipsticks
d. Can be repeated at any time during the study at the discretion of the investigator. All positive urine pregnancy test results must be confirmed by a serum test.
e. S-troponin T, reflex for CPK >500U/l.

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed at the central laboratory.

The investigator must review (initial and date) the results of the clinical safety laboratory tests as soon as possible after receipt of those results. Out-of-range values must be interpreted by the investigator as “not clinically significant” or “clinically significant” with a comment concerning the planned follow-up. Tests for clinically significant out-of-range values must be

repeated, or an appropriate clinical follow-up must be arranged by the investigator and documented on the laboratory report, until the value has stabilised or until the value has returned to a clinically acceptable value (regardless of relationship to IMP). Any value that is out-of-range at the Primary Outcome or Withdrawal Visit and judged clinically significant must be followed according to accepted medical standards for up to 42 days or until the value normalises or stabilises or a diagnosis or reasonable explanation has been established. Any out-of-range values followed after the last protocol-specified contact with the patient will be documented in the patient's medical record.

Clinically significant out-of-range values must be recorded as an adverse event on an *Adverse Event Form*.

The central laboratory will be notified by the sponsor when the biological samples may be destroyed.

9.5.3 Vital Signs

Pulse rate and blood pressure will be measured using a standard digital meter.

Pulse rate and blood pressure will be measured in the following order: supine, sitting, and standing after the patient has rested in each position for at least 3 minutes.

Vital signs must be assessed prior to blood sampling.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form.*

9.5.4 Weight and Waist Circumference

The patients will be weighed wearing light clothing and no shoes. A similar amount of clothing must be worn on each occasion.

Waist circumference should be recorded before the patient's meal and at approximately the same time at each visit. The measurement will be made by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation.

Two waist measurements will be performed. If the two measurements are differing by 1 cm or more, a third measurement will be performed. Waist circumference is the average of all the measurements performed.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form*.

9.5.5 Electrocardiograms (ECGs)

A standard 12-lead ECG will be recorded using digital ECG recording equipment provided to the investigator or, upon agreement, to an external cardiology centre. The ECGs will be transferred digitally to a central ECG laboratory for evaluation. The investigator will be provided with the results and a cardiological interpretation of the ECG from the central ECG laboratory.

The results from the central ECG laboratory will include the RR, PR, QRS, QT, and QT_c intervals.

The investigator has the final decision on the interpretation of the ECG results. Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form*.

ECGs will be recorded according to the time schedule provided in Panel 2.

For *16159A-patients*, additional ECGs will be performed at the time of switching from daily dosing to weekly dosing; 1 ECG should be recorded before the daily dose is switched to weekly dosing (preferably on the day the decision of switching from daily dosing to weekly dosing is taken), and 1 ECG should be recorded the day after the first weekly dose in taken.

9.5.6 Physical Examination

The investigator may appoint a designee to be primarily responsible for performing the physical examinations provided this is permitted according to local regulations. The investigator must take responsibility for reviewing the findings. Whenever possible, the same individual should perform all the physical examinations.

The physical examination (including height at the Screening and Baseline Visit) must, at a minimum, include an examination of appearance, extremities, skin, head, neck, eyes, ears, nose, throat, lungs, chest, heart, abdomen and musculoskeletal system and must be performed by a physician or physician assistant.

Genito-urinary system examinations are often not part of routine psychiatric practice. For most patients, an external inspection of the genitals should be sufficient. A full gynaecological examination should only be performed if warranted by symptoms or medical history. The renal regions will be examined as part of the abdominal examination.

Abnormalities of clinical significance must be recorded as an adverse event on an *Adverse Event Form*.

9.5.7 Safety Assessment Tools

The following safety assessments will be administered:

- C-SSRS – clinician-rated assessing suicidality
- AIMS – clinician-rated assessing abnormal involuntary movements

- BARS – clinician-rated, assessing akathisia
- mSAS – clinician-rated, assessing extrapyramidal symptoms

The C-SSRS will be administered in the local language. The AIMS, BARS and mSAS will be administered in English only. Only scales provided by H. Lundbeck A/S and that have been validated in the language to which they have been translated will be used in this study.

Detailed instructions on how to administer the scales and how to score using the scales will be provided to the site.

9.5.7.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study. The C-SSRS has 4 questions addressing suicidal behaviour, 5 questions addressing suicidal ideation, and sub-questions assessing the severity.

The C-SSRS is available in a *Baseline/Screening* version which is to be used at the Screening Visit and a *Since last visit* version which is to be used at all subsequent visits.

An experienced clinician can use the C-SSRS after a short training session. It takes approximately 5 minutes to administer and rate the C-SSRS.

9.5.7.2 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[25] is a clinician-rated scale designed to assess abnormal involuntary movements (for example, dyskinesia) associated with anti-psychotic drugs. The AIMS consists of 12 items: items 1 to 7 assess the severity of movements in 3 anatomical areas (facial/oral, extremities and trunk); items 8 and 9 assess the global severity and the incapacitation due to the movements; item 10 assesses the patient's awareness of the movements and the distress due to them; items 11 and 12 clarify the patient's dental status. The 12 items are assessed using a neurological examination: items 1 to 9 are rated on a 5-point scale, from 0 (none) to 4 (severe); item 10 is rated on a 5-point scale, from 0 (no awareness) to 4 (aware, severe distress); and items 11 and 12 are rated on a 2-point scale, 0 (no) and 1 (yes). The total score ranges from 0 to 42. The AIMS can be administered by a physician after a short training.

It takes approximately 5 to 10 minutes to administer and score the AIMS.

9.5.7.3 Barnes Akathisia Scale (BARS)

The BARS[26] is a clinician-rated scale designed to assess the presence and severity of drug induced akathisia. The BARS consists of 4 items: one objective item (observed restlessness), two subjective items (patient's awareness of restlessness and related distress), and a global clinical assessment of akathisia. The objective and subjective symptoms are rated on a 4-point scale, from 0 (no symptom) to 3 (severe symptoms). The global clinical assessment is rated on a 6-point scale from 0 (absent) to 5 (severe akathisia). Comprehensive definitions are

provided for each anchor point on the scales. The BARS can be administered by a physician after a short training session.

It takes 10 to 15 minutes to administer and score the BARS.

9.5.7.4 Modified Simpson Angus Scale (mSAS)

The mSAS,[27] is a clinician-rated scale designed to assess the presence and severity of drug-induced parkinsonism. The mSAS consists of 10 items to evaluate gait, rigidity (arms and head), eye-blinking, tremor, salivation and akathisia. The 10 items are assessed using a neurological examination and rated on a 5-point scale, from 0 (absence of the condition) to 4 (most extreme form of the condition). Comprehensive definitions are provided for each anchor point on the scale. The mSAS can be administered by a physician after a short training session.

It takes 10 to 15 minutes to administer and score the mSAS.

9.5.7.5 Rater Qualification and Certification

The C-SSRS should be rated by a clinician (see 9.2.1.8). The AIMS, BARS, and mSAS must only be administrated by physicians having adequate experience in patients with schizophrenia. Any exceptions must be discussed and approved by Lundbeck.

Only raters who have been already trained and certified in studies 16159A and 16323A are allowed to rate the patients in study 16159B. New raters joining study 16159B will be trained and certified using the same certification processes as in study 16159A.

Documentation of training and certification will be delivered to the raters for archiving in the investigator study master file (TMF). No patient may be rated before the documentation has been delivered.

Rater training and certification will be conducted by a third party vendor selected by the sponsor.

Each site should have a minimum of 2 certified raters per scale in order to provide back-up for each other. Any exceptions must be discussed and approved by Lundbeck.

9.6 Order of Assessments

The scales should preferably be administered in the following order at the applicable visits:

Screening Visit:
- PANSS, PSP, and C-SSRS
- CGI-S

All visits other than Screening Visit:

- TooL and MSQ
- PANSS, NSA-4, QLS, PSP, C-SSRS and WoRQ
- CGI-S
- AIMS, BARS, and mSAS
- HEA

9.7 Treatment Compliance

The responsible study personnel will dispense the IMPs. Accountability and compliance verification should be documented in the patient's source documents. Patients must be counselled on the importance of taking the study medications as directed at all study visits.

The medical monitor should be contacted if the investigator is uncertain whether a patient's lack of compliance warrants withdrawal from the study.

Patients must be counselled on the importance of taking the IMP as directed at all study visits.

9.8 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 110 mL during the study.

Additional blood samples may be required if the original blood samples are not viable or if re-testing is required.

The biobank blood samples and any derived material for possible future exploratory pharmacogenetic analyses will be destroyed ≤15 years after the end of the study (see definition in section 8.6) by a Central Laboratory.

The biobank blood samples and any derived material for possible future exploratory gene expression profiling and metabolic or proteomic biomarker assessments will be destroyed ≤10 years after the end of the study (see definition in section 8.6) by a Central Laboratory.

All samples for pharmacokinetic assessment will be retained at the bioanalytical facility until the results have been reported. The samples will subsequently be destroyed by the responsible analytical laboratory. The bioanalytical lab will retain the samples until the bioanalytical report is final. The ISM will be notified that the samples are to be destroyed, and the documentation for sample destruction will be kept in the bioanalytical study file.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[28]

Adverse event – is any untoward medical occurrence in a clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including clinically significant out-of-range values from relevant tests, such as clinical safety laboratory tests, vital signs, ECGs), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

Serious adverse event (SAE) – is any adverse event that:

- results in death
- is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically important (this refers to an event that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent any of the SAEs defined above)

Examples of medically important events are intensive treatment for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Planned hospitalisations or surgical interventions for a condition that existed before the patient signed the *Informed Consent Form* and that did not change in intensity are not SAEs. Emergency room visits that do not result in admission to the hospital are not necessarily SAEs; however, they must be evaluated to determine whether they meet any of the SAE definitions (for example, life-threatening or other serious [medically important] event).

The C-SSRS has 5 questions addressing suicidal ideation. If level 4 or 5 has been answered “yes”, it must be considered by the investigator whether an SAE should be reported.

Non-serious adverse event – is any adverse event that does not meet the definition of an SAE.

If there is any doubt as to whether an adverse event meets the definition of an SAE, a conservative viewpoint must be taken, and the adverse event must be reported as an SAE.

Suspected unexpected serious adverse reaction (SUSAR) – is any adverse event that is assessed as serious, unexpected (its nature or intensity is not consistent with the current version of the Investigator's Brochure for Lu AF35700) and related to Lu AF35700 by either the investigator or the sponsor.

Overdose – is a dose taken by a patient that exceeds the dose prescribed to that patient. Any overdose (and associated symptoms) must, at a minimum, be recorded as a non-serious adverse event.

10.1.2 Adverse Event Assessment Definitions

Assessment of Intensity

The investigator must assess the *intensity* of the adverse event using the following definitions, and record it on the *Adverse Event Form*:

- *Mild* – the adverse event causes minimal discomfort and does not interfere in a significant manner with the patient's normal activities.
- *Moderate* – the adverse event is sufficiently uncomfortable to produce some impairment of the patient's normal activities.
- *Severe* – the adverse event is incapacitating, preventing the patient from participating in his or her normal activities.

Assessment of Causality

The investigator must assess the *causal relationship* between the adverse event and the IMP using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Probable* – the adverse event has a strong temporal relationship to the IMP or recurs on rechallenge, and another aetiology is unlikely or significantly less likely.
- *Possible* – the adverse event has a suggestive temporal relationship to the IMP, and an alternative aetiology is equally or less likely.
- *Not related* – the adverse event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the adverse event).

An adverse event is considered causally related to the use of the IMP when the causality assessment is *probable* or *possible*.

Assessment of Outcome

The investigator must assess the *outcome* of the adverse event using the following definitions, and record it on the *Adverse Event Form* and the *Serious Adverse Event Form* (if applicable):

- *Recovered* – the patient has recovered completely, and no symptoms remain.
- *Recovering* – the patient's condition is improving, but symptoms still remain.

- *Recovered with sequelae* – the patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally, but has some motor impairment).
- *Not recovered* – the patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
- *Death*

10.1.3 Study-specific Adverse Event Definitions

10.2 Pregnancy

Although not necessarily considered an adverse event, a pregnancy in a patient in the study must be recorded on an *Adverse Event Form*, as well as on a *Pregnancy Form* (paper), even if no adverse event associated with the pregnancy has occurred. Pregnancies must be reported to Lundbeck using the same expedited reporting timelines as those for SAEs.

An uncomplicated pregnancy should not be considered an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion (for example, hospitalisation) must be indicated on the *Serious Adverse Event Form*. Examples of pregnancies to be reported as SAEs (medically important) are spontaneous abortions, stillbirths, and malformations.

The investigator must follow up on the *outcome* of the pregnancy and report it on a *Pregnancy Form* (paper). The follow-up must include information on the neonate at least up until the age of 1 month.

If the partner of a man participating in the study becomes pregnant, the *outcome* of the pregnancy should be followed if the partner agrees. The partner must sign an *Informed Consent Form* to allow the investigator to collect information to report to Lundbeck.

10.3 Recording Adverse Events

Adverse events (including pre-treatment adverse events) must be recorded on an *Adverse Event Form*. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours); intensity; causal relationship to IMP; action taken; and outcome. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose). If the intensity changes during the course of the adverse event, this must be recorded on the *AE Intensity Log*.

If the adverse event is *serious*, this must be indicated on the *Adverse Event Form*. Furthermore, the investigator must fill out a *Serious Adverse Event Form* and report the SAE to Lundbeck immediately (within 24 hours) after becoming aware of it (section 10.4).

Adverse events, including clinically significant out-of-range clinical safety laboratory test values and findings from for example, ECGs, must be recorded individually, except when

considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

10.4 Reporting Serious Adverse Events

The investigator must report SAEs to Lundbeck immediately (within 24 hours) after becoming aware of them by completing a *Serious Adverse Event Form*.

The initial report must contain as much information as possible and, if more information about the patient's condition becomes available, the *Serious Adverse Event Form* must be updated with the additional information.

If the investigator cannot report the SAE in Rave®, then he or she must complete and sign the *Serious Adverse Event Fallback Form* and send it to:

Pharmacovigilance (PV)
Fax: +45 36 30 99 67
e-mail: safety@lundbeck.com

Lundbeck will assume responsibility for reporting SAEs to the authorities in accordance with local regulations.

It is the investigator's responsibility to be familiar with local requirements regarding reporting SAEs to the IEC or IRB and to act accordingly.

Lundbeck will assume responsibility for reporting SUSARs to the authorities in accordance with local regulations. In those Member States of the European Union that have implemented the European Union *Clinical Trials Directive*[29] and in Norway, Liechtenstein, and Iceland, that is, in the countries where unblinded expedited safety reporting is required, Lundbeck will also assume responsibility for reporting SUSARs to the ethics committees.

Lundbeck will assess the expectedness of SAEs and inform the investigator(s) about SUSARs, at 6 monthly blinded SUSAR listings. CIOMS-I reports for SUSARS are not normally distributed to investigators in those countries where SUSAR listings are sufficient. However, if the CIOMS-I reports are required (for example, by the local EC/IRB/REB), they will be sent to the investigator.

10.5 Treatment and Follow-up of Adverse Events

Patients with adverse events must be treated in accordance with usual clinical practice at the discretion of the investigator.

Non-serious adverse events must be followed up until resolution or the safety follow-up assessment, whichever comes first. At the safety follow-up, information on new SAEs, if any, and stop dates for previously reported adverse events must be recorded.

It is the responsibility of the investigator to follow up on all SAEs until the patient has recovered, stabilised, or recovered with sequelae, and to report to Lundbeck all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultations.

SAEs that are spontaneously reported by a patient to the investigator after the safety follow-up assessment must be handled in the same manner as SAEs that occur during the study. These SAEs will be captured in the PV database.

Patients with clinically significant out-of-range clinical safety laboratory test values at the Primary Outcome or Withdrawal Visit must be followed in accordance with usual clinical practice and be scheduled for a Safety Follow-up Visit to allow for a medical examination and/or blood sampling (see section 8.5).

Patients who withdraw due to elevated AST or ALT values (see section 5.4) must be followed until the values normalise or stabilise or a diagnosis or a reasonable explanation has been established. Additional medical examinations (for example, ultrasound scanning and/or sampling for serology, conjugated bilirubin, INR) should be considered. A gastroenterology or hepatology consultation should also be considered.

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms (eCRFs)

eCRFs will be used to collect all the data related to the study, except the external data described in section 11.1.3.

The eCRFs use third party software (Rave®) to capture data via an on-line system on a computer. Data related to the study will be recorded electronically in a central database over encrypted lines, and all entries and modifications to the data will be logged in an audit trail. Access to the system will only be granted after appropriate and documented training. Written instructions for using the system will be provided along with the training.

Electronic signatures will be used where signatures are required on pages and/or visits. Automated data entry checks will be implemented where appropriate; other data will be reviewed and evaluated for accuracy by the CRA. All entries, corrections, and changes must be made by the investigator or a delegate.

11.1.2 Patient Binders

11.1.2.1 Use of Patient Binders

Lundbeck may provide a *Patient Binder* for each patient. The *Patient Binder* contains different types of source documents, organised by visit and type. A ballpoint pen with waterproof ink must be used to enter information in the *Patient Binder*.

11.1.2.2 Rating Scales and Patient-reported Outcomes (PROs)

The *Patient Binder* contains paper versions of the rating scales and PROs. They will be completed by the rater(s) and patient, respectively. The data will be transcribed to the *Scoring Sheets* in the eCRF by the investigator or a delegate.

The rater(s) must verify that all the entries in the *Scale Section* are accurate and correct by signing and dating the relevant pages.

The patients will be asked to complete the PROs in their local language. The patients' responses may only be corrected by the patient.

11.1.2.3 Serious Adverse Event Fallback Forms

Serious Adverse Event Fallback Forms must be used when the eCRF cannot be accessed.

11.1.3 External Data

All electronic data will be transferred using a secure method accepted by Lundbeck.

The electronic data received from the following vendors will be kept in a secure designated storage area outside the eCRF:

- The clinical safety laboratory test results will be transferred by central laboratory.
- The ECG results will be transferred by the central ECG service provider.
- If any electronic assessment tools (i.e PANSS, CGI-S, PSP, SAS, AIMS, BARS, NSA-4, QLS, WorQ, C-SSRS) and/or patient reported outcomes (i.e TooL, MSQ and HEA) will be used, the results will be transferred by the designated vendor.

11.2 Retention of Study Documents at the Site

11.2.1 eCRF Data

If a site closes before the study has been completed, the investigator will continue to have read-only access to the eCRF. If a site closes after the study has been completed, the investigator will no longer have read access to the eCRF. Instead, each site will be provided with a CD-ROM containing the data related to the site (including eCRF data, queries, and the audit trail). As a CD-ROM is not considered a durable medium and may therefore not be

readable for the full retention period (for example, 15 years [if required by the applicable regulatory requirements]), it is possible for the investigator to request a new CD-ROM with the data related to the site.

11.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF for at least 15 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer.

Since off-site storage is used, a study-specific binder will remain at the site after the other study-specific documents have been shipped for off-site storage. This binder is considered part of the investigator TMF and must be kept in a secure place by the site for the required period of time. The binder must contain, at a minimum, the following documents: a copy of the *Investigator TMF Index*, a certified copy of the *Patient Identification Code List*, and a *Retrieval Form*.

Lundbeck will notify the investigator in writing when the required storage period has expired and when the documents may be destroyed according to regulations.

12 Monitoring Procedures

Prior to including patients in the study, the investigator must sign a source data agreement that identifies the source documents (original documents, data, and records) at the site. The document will also list which data may be recorded directly on the eCRFs or any electronic clinical outcome assessment electronic clinical outcome assessment (eCOA).

If the investigator does not have a patient's medical records, the investigator must attempt to obtain copies or a written summary of relevant medical records from the doctor who had treated the patient earlier and include the pertinent documentation in the patient's medical records at the site. The investigator must obtain medical records documenting the patient's lifetime (schizophrenia) episodes and general medical history for the 3 months prior to the study.

During the study, the CRA will visit the site to ensure that the protocol is being adhered to and that all issues are being recorded, to perform source data verification, and to monitor IMP accountability. The visit intervals will depend on the outcome of the remote monitoring of the eCRFs, the site's recruitment rate, and the compliance of the site to the protocol and *Good Clinical Practice*. In addition, the CRA will be available for discussions by telephone.

Source data verification requires that the CRA be given direct access to all the source documents. Direct access includes permission to examine, analyse, and verify any records and reports that are important for the evaluation of the study.

13 Audits and Inspections

Authorised personnel from Global Clinical Quality Assurance at Lundbeck and quality assurance personnel from business partners may audit the study at any time to assess compliance with the protocol and the principles of *Good Clinical Practice* and all other relevant regulations.

The patients must be informed that authorised personnel from Lundbeck may wish to review their medical records. The investigator must be aware and the patients must be informed that representatives from regulatory authorities may also wish to inspect source data, such as medical records.

The investigator must notify Lundbeck, without delay, of an announced inspection by a regulatory authority.

During audits and inspections, the investigator must permit direct access to all the source documents, including medical records and other documents pertinent to the study.

During audits and inspections, the auditors and inspectors may copy relevant parts of medical records. No personal identification apart from the screening number will appear on these copies.

Patient data will not be disclosed to unauthorised third parties, and patient confidentiality will be maintained at all times.

14 Protocol Compliance

Lundbeck has a “no-waiver” policy, which means that permission will not be given to deviate from the protocol.

If deviations occur, the investigator must inform the CRA and they must review, discuss, and document the implications of the deviation.

15 Study Termination

Lundbeck or a pertinent regulatory authority may terminate the study or part of the study at any time. The reasons for such action may include, but are not limited to:

- safety concerns
- proven lack of efficacy of the IMP in other studies

If the study is terminated or suspended, the investigator must promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or sponsor must promptly inform the IEC or IRB and provide a detailed written explanation. The pertinent regulatory authorities must be informed in accordance with national regulations.

If the risk/benefit analysis changes after the termination of the study, the new evaluation must be provided to the IEC or IRB if it will have an impact on the planned follow-up of the patients who participated in the study. If so, the actions needed to protect the patients must be described.

16 Endpoints

16.1 Primary Endpoint(s)

- Primary safety and tolerability endpoints:
  - Adverse events
  - Absolute values, changes values from baseline and potentially clinically significant values in:
    - Clinical safety laboratory tests
    - Body weight, BMI, and waist circumference
    - Vital signs (systolic blood pressure, diastolic blood pressure, and pulse)
    - ECG parameters (ventricular rate, RR, PR, QRS, QT, and QTcF)

16.2 Exploratory Endpoint(s)

- Exploratory safety and tolerability endpoints:
  - Mean change from baseline in AIMS, BARS and mSAS total scores
  - C-SSRS categorisation
- Exploratory effectiveness endpoints:
  - Psychotic symptoms
    - Mean change from baseline in PANSS total score
    - Mean change from baseline in PANSS subscale scores (PANSS Negative Symptoms subscale, PANSS Positive Symptoms subscale, PANSS General Psychopathology subscale)
  - Negative symptoms
    - Mean change from baseline in NSA-4 total score
  - Global clinical impression
    - Mean change from baseline in CGI-S score
  - Andreason symptoms remission rate
    - Binary variable (Y/N) of remission rate (simultaneous ratings of mild or less on PANSS specific items: P1, G9, P3, P2, G5, N1, N4, and N6) at Week 52 Visit
  - Quality of life and functioning
    - Mean change from baseline in QLS score
    - Mean change from baseline in TooL score
    - Mean change from baseline in WorQ score
    - Mean change from baseline in PSP total score

- Treatment satisfaction
  - Mean change from baseline in MSQ score
- Health care resource used during the 52-week study period

17 Statistical Methodology

17.1 Responsibilities

The Department of Biostatistics, H. Lundbeck A/S will perform the statistical analyses described below.

17.2 Analysis Sets

The following analysis sets are defined.

- all-patients-treated set (APTS) – all patients who took at least one dose of Lu AF35700 in study 16159B.
- full analysis set (FAS) –all patients in the APTS who had at least one valid post baseline effectiveness assessment in study 16159B.

The APTS will mainly be used for presentations of safety data whereas the FAS will be used for effectiveness data.

17.3 Descriptive Statistics

In general, summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables and counts and, if relevant, percentages will be presented for categorical variables.

For patients coming from 16159A, summaries will be prepared with respect to two baselines:

- Baseline I: Baseline just prior to randomisation in study 16159A (Baseline 2 in 16159A)
- Baseline II: Baseline in study 16159B.

Unless otherwise specified, baseline will be Baseline II.

Summaries will be prepared overall and by the previous treatment (treatment group in the studies feeding into this extension study or previous treatment for patients not included in any Lu AF35700 study before). In order not to have too many “previous treatments”, these will be grouped into the following categories:

- Lu AF35700
- Risperidone/Olanzapine (16159A patients)
- Quetiapine
- Previous treatment for patients not included in any Lu AF35700 study before

To explore the safety and effectiveness of daily dosing with Lu AF35700, separate displays will be prepared for patients only receiving daily dosing in this study.

17.4 Patient Disposition

Patient disposition will be summarised by reason for withdrawal and other relevant parameters and include the number of patients who completed and the number of patients who withdrew from the study.

17.5 Demographics and Other Baseline Characteristics

Demographics (sex, age, race), and other baseline characteristics will be summarised.

17.6 Recent and Concomitant Medication

Recent and concomitant medication will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name.

17.7 Exposure and Compliance

Exposure and compliance will be calculated per patient and summarised.

In particular, the amount of weekly dosing, frequency, duration, and reasons for initiation and termination, will be summarised.

17.8 Effectiveness Analyses

Effectiveness assessment will be summarised descriptively using Observed Cases (OC). Summaries will be performed with respect to both Baseline I and Baseline II. On an exploratory basis, the maintenance of effectiveness will be analysed using Mixed Models for Repeated Measurements (MMRM).

Quality of life, treatment satisfaction and health care resource utilization will be summarised.

Based on the FAS and observed cases (OC), the effectiveness endpoints will be analysed using a mixed model for repeated measurements (MMRM) with an unstructured covariance structure. The model will include terms for country, baseline 1/2 score visit, and previous treatment.

17.9 Safety Analyses

17.9.1 Analysis of Adverse Events

Adverse events will be classified according to the time of onset of the adverse event:

- *pre-study adverse event* – an adverse event that starts before the date of first dose of IMP in study 16159B.
- *Treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity on or after the date of first dose of Lu AF35700 in study 16159B.

Adverse events, sorted by system organ class (SOC) and preferred term, will be summarised.

Specific tables of adverse events after weekly dosing will be prepared. Displays of all events while on weekly dosing, as well as events seen shortly after initiation of weekly dosing will be prepared.

Allocation of TEAEs to Treatment Periods

TEAEs may be allocated into study periods (these will be defined in the *Statistical Analysis Plan*).

Where relevant, Kaplan-Meier plots of time to TEAEs, will be prepared.

17.9.2 Analysis of Other Safety Endpoints

The clinical safety laboratory test values, body weight, BMI and waist circumference, vital signs, and ECG parameters will be summarized. Potentially clinically significant (PCS) values will be flagged and summarized.

Mean change from baseline in AIMS, BARS and mSAS total scores will be summarized.

The C-SSRS will be summarized descriptively.

17.10 Interim Analyses

No interim analyses are planned.

17.11 Sample Size and Power

No formal sample size calculation has been performed for the present study.

Approximately 400 patients with schizophrenia are planned to be enrolled in total in order to provide relevant long-term safety data. It is assumed that about 270 patients will come from study 16159A, 30 patients from study 16323A, and an additional 100 patients who need to change their antipsychotic treatment will be included. The distribution of the number of patients may be adjusted based upon the recruitment rate in each group. With approximately

400 patients included, it will be possible to obtain solid information on long-term safety of treatment with Lu AF35700.

To ensure sufficient exposure to the daily dosing regimen, the number of patients who completed study 16159A and who can be treated with the weekly dosing regimen will be limited to 50 patients.

17.12 Statistical Analysis Plan

A *Statistical Analysis Plan* describing the handling of data issues and the planned statistical analyses in more detail will be prepared by the Department of Biostatistics, H. Lundbeck A/S.

18 Clinical Study Report and Publications

18.1 Clinical Study Report

Upon completion of the study, a *Clinical Study Report* will be prepared by the Department of Medical Writing, H. Lundbeck A/S.

18.2 Data Ownership

The data collected in this study are the property of Lundbeck.

18.3 Publications

The results of this study will be submitted for publication.

The primary publication based on this study must be published before any secondary publications are submitted for publication.

Authors of the primary publication must fulfil the criteria defined by the International Committee of Medical Journal Editors (ICMJE).[30]

19 Indemnity and Insurance

In the event of study-related injuries or deaths, insurance for the patients and indemnity of the investigators and those of their employees, servants, or agents whose participation in this study has been documented are provided. Insurance and liability will be in accordance with applicable laws and *Good Clinical Practice*.

20 Finance

20.1 Site Agreement

The financial agreements for the site are addressed in one or more documents. Both parties must sign the agreements before the site is initiated.

20.2 Financial Disclosure

All the investigators, including sub-investigators, and raters participating in the study must complete a *Financial Disclosure Form* in order to comply with the United States Food and Drug Administration (FDA) *Financial Disclosure* requirements.

20.3 Equipment

Equipment owned or rented by Lundbeck that has been provided to the site for use during the study must be returned at the end of the study.

References

1. Carpenter WT Jr, Buchanan RW. Schizophrenia. N Engl J Med. 1994; 330: 681-690.
2. Adler LA, Angrist B, Reiter S, Rotrosen J. Neuroleptic-induced akathisia: a review. Psychopharmacology (Berl). 1989; 97: 1-11.
3. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry. 1991; 148: 1474-1486.
4. H. Lundbeck A/S. Investigator's Brochure: Lu AF35700, current version.
5. H. Lundbeck A/S. Interventional, open-label, positron emission tomography (PET) study investigating D2 dopamine receptor occupancy after multiple oral dosing of Lu AF35700 in healthy men using [11C]-PHNO as tracer compound, reporting.
6. H. Lundbeck A/S. Analysis of D2 receptor occupancy versus plasma concentration of Lu AF35700 and Lu AF36152 and simulation of D2 receptor occupancy time profiles. 23 Oct 2014.
7. EMA. Committee for Medicinal Products for Human (CMPH). Guideline on clinical investigation of medicinal products in the treatment of schizophrenia. EMA/CHMP/40072/2010. 2011.
8. World Medical Association (WMA). Declaration of Helsinki: Ethical principles for medical research involving human subjects. [Internet] wma.net/en/30publications/10policies/b3/index.html
9. ICH. ICH Harmonised Tripartite Guideline E6 (R1): Guideline for Good Clinical Practice. 1996.
10. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry. 2007; 68 (Suppl 4): 8-13.
11. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987; 13(2): 261-276.
12. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand. 2003; Suppl 416: 16-23.
13. Alphs L, Morlock R, Coon C, van Willigenburg A, Panagides J. The 4-item negative symptom assessment (NSA-4) instrument: A simple tool for evaluating negative symptoms in schizophrenia following brief training. Psychiatry. 2010; 7: 26-32.
14. Nasrallah H, Morosini, PL, Gagnon DD. Reliability, validity and ability to detect change of the Personal and Social Performance scale in patients with stable schizophrenia. Psychiatry Res. 2008; 161(2): 213-224.
15. Heinrichs DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull. 1984; 10: 388-398.
16. Potkin SG, Bugarski-Kirola D, Edgar CJ, Soliman S, Le Scouiller S, Kunovac J et al. Psychometric evaluation of the Work Readiness Questionnaire in schizophrenia. CNS Spectr. 2014; Oct 1: 1–8.

17. Vernon MK, Revicki DA, Awad AG, Dirani R, Panish J, Canuso CM et al. Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. Schizophr Res. 2010; 118(1-3): 271-278.
18. Lindström E, Jönsson L, Berntsson A. A patient perspective on side effects of antipsychotic therapy: the TooL instrument. Value Health. 2009; 12: A361.
19. Novick D, Haro JM, Suarez D, Vieta E, Naber D. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. Schizophr Res. 2009; 108(1-3): 223-230.
20. European Parliament and Council of the European Union. Directive 95/46/EC: Protection of individuals with regard to the processing of personal data and on the free movement of such data. 24 October 1995. Official Journal of the European Communities L 281, 23 November 1995.
21. Kay SR, Opler RA, Fiszbein A. The Structured Clinical Interview for Positive and Negative Syndromes of Schizophrenia Multi-Health Systems, New York 1992.
22. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Guideline on bioanalytical method validation. EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2. 2015.
23. United States Food and Drug Administration (FDA). Guidance for Industry: Bioanalytical method validation. 2001.
24. European Agency for the Evaluation of Medicinal Products (EMEA). Committee for Proprietary Medicinal Products (CPMP). Position paper on terminology in pharmacogenetics. EMEA/CPMP/3070/01. 21 November 2002.
25. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised ed. Washington, DC, US Department of Health, Education, and Welfare, 1976.
26. Barnes TRE. A rating scale for drug-induced akathisia. Br. J. Psychiatry. 1989; 154: 672–676.
27. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970; 212: 11-19.
28. ICH. ICH Harmonised Tripartite Guideline E2A: Clinical safety data management: definitions and standards for expedited reporting. 1994.
29. European Parliament and Council of the European Union. Directive 2001/20/EC: Approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 4 April 2001. Official Journal of the European Communities L 121, 1 May 2001.
30. International Committee of Medical Journal Editors (ICMJE). [Internet] icmje.org/urm_main.html. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. August 2013.

Appendix I

Clinical Study Protocol Authentication and Authorisation

Clinical Study Protocol
Authentication and Authorisation

Study title:	Interventional, open-label, flexible-dose, long-term safety study of Lu AF35700 in adult patients with schizophrenia
Study No.:	16159B
Edition No.:	1.0
Date of edition:	24 May 2016

This document has been signed electronically. The signatories are listed below.

Authentication

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

International study manager:	[redacted]
Clinical research scientist:	[redacted]
Head, Biostatistics:	[redacted]
Head of Risk Management (PV):	[redacted]

Authorisation

I hereby confirm that I am of the opinion that the ethical and scientific basis of this study is sound.

Vice President, Clinical Research & Development, Psychiatry:	[redacted]

Appendix II
Recent and Concomitant Medication:
Disallowed or Allowed with Restrictions

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

In the table below disallowed recent and concomitant medications are listed, including any restrictions with respect to their use prior to and during the study.

Disallowed and restricted medications during the study

Drug Class	Details
Analgesics	– Opioid analgesics are not allowed, except for brief episodic use during emergency procedures or appropriate indication (e.g. tooth extraction) and not within 24 hour before a study visit. – NSAIDs are prohibited as chronic use; NSAIDs may be used episodically.
Anticholinergics	– The use of anticholinergic medication as prophylaxis of extrapyramidal symptoms should be avoided. – In case of need of rescue medication, the use of multiple anticholinergic medications concurrently is prohibited. – The allowed rescue medications are the following: benzotropine (up to 4 mg/day p.o. or i.m.), biperiden (up to 8 mg/day p.o. or i.m.) and thrihexyphenidyl (up to 10 mg/day p.o. or i.m.). – Administration of anticholinergics less than 8 hours prior a scheduled visit is not allowed.
Anticonvulsants	– Prohibited during the study
Antidepressants	– Prohibited during the study
Antihistamines	– Antihistamines except loratadine, desloratidine, cetirizine, levocetirizine, mizolastine and fexofenadine are prohibited.
Antipsychotics	– Depot or long-acting injectable antipsychotics are not allowed as current treatment. – Current oral antipsychotics to be down tapered and discontinued as indicated in Panel 3. – Oral antipsychotics other than LuAF35700 is disallowed during the study.
Anxiolytics and hypnotics	– If the patient receives anxiolytic or hypnotic therapy during study 16159A, this medication may continue. A careful down tapering of anxiolytic or hypnotic treatment should be performed if a discontinuation has been decided. – In case of need of rescue medication for anxiety, dose adjustment of currently prescribed anxiolytic medication is recommended if applicable. If new medication is initiated, short-acting benzodiazepines such as lorazepam (up to 3 mg/day, orally or intramuscularly), oxazepam (up to 45 mg/day, orally), and alprazolam (up to 1.5 mg/day) are recommended. – In case of need of rescue medication for sleep disorders, short acting hypnotics such as zolpidem (up to 5 mg/day for immediate release formulations and 6.25 mg/day for extended release formulations, orally) and zopiclone (up to 7.5 mg/day) are recommended. – Administration of anxiolytics or hypnotics less than 8 hours prior a scheduled visit is not allowed.
Barbiturates	– Prohibited during the study

Drug Class	Details
Dopamine depleting agents	– Prohibited during the study
Hormones	– Prohibited except for thyroid hormone replacement, contraceptives (oral, patch), estrogen and progesterone replacement therapy as well as benign prostatic hyperplasia treatment.
Hydroxyzine and diphenhydramine (not allowed for the treatment of agitation, anxiety, insomnia or EPS)	– Except for short term treatment (<14 days) of allergy.
Mood stabilizers	– Prohibited during the study
Non-benzodiazepine sleep aids	– Prohibited during the study
Propranolol (for akathisia or tremor)	– Prophylaxis treatment should be avoided. – In case of need of rescue medication a maximum dose of 60 mg/day is allowed. – If propranolol is prescribed for cardiovascular reasons at doses greater than 60 mg/day, the eligibility of the patients should be discussed with the Medical Monitor. – Administration of propranolol less than 8 hours of a scheduled visit is not allowed.
Psychotropic agents not otherwise specified	– Prohibited during the study – Cough preparations containing ephedrine, pseudoephedrine and codeine are allowed for treatment duration for a maximum of 1 week.
Steroids	– Systemic use is prohibited, inhaled and topical use is allowed.
Varenicline	– Prohibited during the study
Vitamins, nutritional supplements, and non-prescritpion herbal preparations	– Prohibited during the study, unless approved in advance by the Medical Monitor.