Clinical Study Protocol

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

Lu AF35700

Study No.:	16159A
EudraCT/IND No:	2014-003569-12 (EU) / 116,335 (US)
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
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Synopsis – Study 16159A

Sponsor H. Lundbeck A/S	**Investigational Medicinal Product** Lu AF35700	**EudraCT/IND No.** 2014-003569-12 / 116,335
Title of Study Interventional, randomised, double-blind, active-controlled, fixed-dose study of Lu AF35700 in patients with Treatment-resistant Schizophrenia		
Study Site(s) and Number of Patients Planned 130 sites are planned in approximately 18 countries (in-/outpatient clinics) 675 patients are planned for randomisation with 225 patients per treatment group in Period B		
Objectives • Primary objective: – to evaluate the efficacy of 10 and 20 mg/day of Lu AF35700 on schizophrenia symptoms in patients with treatment-resistant schizophrenia (TRS) • Secondary objectives: – to evaluate the efficacy of 10 and 20 mg/day of Lu AF35700 on functioning of patients with TRS • Exploratory objectives: – to explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on quality of life – to explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on treatment satisfaction – to explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on tolerability – to explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on negative symptoms • Safety objective: – to evaluate the safety and tolerability of 10 and 20 mg/day of Lu AF35700 in patients with TRS		

Study Methodology

- This is an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, active-controlled, fixed-dose study.
- Efficacy of Lu AF35700 will be assessed by testing for superiority versus an active control in patients not responding adequately to the active control.
- The total study duration per patient from Screening to the end of Follow-Up will be approximately 25 weeks.
- The study will consist of 4 Periods:

Screening Period

Patients will enter a Screening Period of 21 days to assess eligibility.

Period A – Prospective Confirmation Period (6 weeks)

Patients who meet the pre-specified selection criteria, including the criteria for treatment resistance, will enter a single (patient)-blinded treatment period with risperidone or olanzapine to confirm their resistance to antipsychotic treatment at Baseline 1. Patients will be initiated on risperidone 2 mg/day and up-titrated to 6 mg/day by the end of the first week, except if they have failed on risperidone (or 9-OH-risperidone; Invega™) in the most recent treatment trial, in which case patients will be initiated on olanzapine at 5 mg/day and up-titrated to 15 mg/day by the end of the first week. Current antipsychotic medication will be down-tapered within the first 7 days of this treatment period. Patients will receive either risperidone 6 mg/day or olanzapine 15mg/day for the subsequent week and thereafter either risperidone 4 or 6 mg/day or olanzapine 15 or 20mg/day for the subsequent four weeks, which can be increased for efficacy or decreased for tolerability at 1-week intervals, between Weeks 2 and 4, according to the investigator's clinical judgement. Patients will be treated with at least 6 mg/day of risperidone (or with 4 mg / day in case the dose of 6 mg was not tolerated and had to be reduced) or with at least 15 mg/day of olanzapine for the last 2 weeks. Patients currently treated with 'depot' antipsychotic medications can, after signing the ICF, be down-tapered by skipping one full treatment cycle plus 3 days before Baseline 1. Patients who do not fulfil the inclusion criteria for Period B will be withdrawn from the study. If the patient is withdrawn during Period A, the investigator will have the option to continue the patient on the treatment assigned during Period A, as prescribed by the investigator, or discontinue IMP.

Period B –Double-blind Treatment Period (10 weeks)

Patients who fulfil the inclusion criteria for lack of clinically relevant improvement during Period A will be considered treatment-resistant and enter the double-blind treatment period (Period B) at Baseline 2. The specific inclusion criteria for Period B will be blinded to the investigators. Patients will be randomly assigned (1:1:1) to 10 weeks of double-blind treatment with either Lu AF35700 10 mg/day, Lu AF35700 20 mg/day or to continue the treatment allocated in Period A at the dose set at last visit of Period A (Week 4). The randomisation will be stratified by country and Period A therapy (risperidone or olanzapine). No dose adjustments will be allowed during Period B. For patients randomised to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion during the initial 7 days of the double-blind treatment period (Period B).

Safety Follow-Up Period (6 weeks)

All patients (except patients, who continue in the extension study), including patients with a clinically relevant improvement, patients who have completed the treatment period and those who withdraw will be scheduled for a Safety Follow-up Visit at the clinic for safety assessments 6 weeks after the last dose of IMP.

- Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will be asked to attend an Efficacy Follow-up Visit at the date of their last scheduled visit of Period B (study Week 16) for the assessment of efficacy, safety and concomitant medication. The study design is presented in Panel 1 and the scheduled assessments are summarised in Panel 2.
- The randomisation rate will be monitored during the study.

Target Patient Population

The target population for the current study is patients with treatment-resistant schizophrenia.

Inclusion Criteria – Period A

- The patient has schizophrenia, diagnosed according to DSM-5™ and confirmed by the Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorder Studies (MINI-Schz).
- The patient is a man or woman, aged ≥18 years.
- The patient is either an inpatient at a psychiatric setting or outpatient consulting a psychiatrist.
- The patient has been treated with adequate dose(s) and agent(s) of antipsychotic treatment for at least 2 weeks prior to Screening.
- The patient has failed to show an adequate response in the level of psychotic symptoms despite at least one treatment trial with an adequate dose of an antipsychotic agent prescribed for an adequate time (at least lasting for 6 weeks) during 2 years prior to Screening.
- The patient has a PANSS total score of ≥ 80 and a score of ≥4 on at least 2 of the following PANSS items (at Screening and at the first visit of Period A [Baseline 1]):
  - P2 – Conceptual disorganization
  - P3 – Hallucinatory behaviour
  - P6 – Suspiciousness/persecution
  - G9 - Unusual thought content
- The patient has a CGI-S score of ≥4 at Screening and at the first visit of Period A (Baseline 1).

Inclusion criteria - Period B

- The inclusion criteria for Period B will be blinded to investigators.
- The inclusion criteria for Period B are described in the *Clinical Study Protocol Addendum - Unmasked Information).*

Investigational Medicinal Products, Doses and Mode of Administration

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

Risperidone: 2, 4, and 6 mg/day, encapsulated tablets, orally

Olanzapine: 5, 10, 15, and 20 mg/day, encapsulated tablets, orally

Placebo: Encapsulated tablets, orally

In order to reduce biases associated with changes in treatment between the study periods and for blinding purposes during the down titration of risperidone or olanzapine, patients will be given two identical capsules throughout both treatment periods.

Administration: Once daily, the two capsules will be taken together in the morning or evening. At Visit 2 (Baseline 1), the first dose is to be taken the day after study medication has been dispensed to the patient.

Period A – Prospective confirmation period

- Patients will be initiated on the lowest dose and titrated up to 6 mg/day risperidone or 15 mg/day olanzapine during the first week according to the following scheme:
  - Risperidone: 2 mg/day for the first 2 days; 4 mg/day for the next 2 days; 6 mg/day for the last 3 days, encapsulated tablets, orally.
  - Olanzapine: 5 mg/day for the first 2 days; 10 mg/day for the next 2 days; 15 mg/day for the last 3 days, encapsulated tablets, orally.
- Dose adjustments for efficacy or tolerability are allowed between weeks 2 and 4 to either 4 or 6 mg/day of risperidone or to either 15 or 20 mg/day olanzapine according to the investigator's clinical judgement.

Period B – Double-blind treatment period

- Patients will be initiated on Lu AF35700 10 mg/day without titration or 20 mg/day starting with 10 mg for 4 days followed by 20 mg/day thereafter.
- Patients randomised to the continued treatment (risperidone or olanzapine) will be treated with the same dose as set at last visit of Period A (Week 4). No dose adjustment will be allowed in Period B.
- For patients randomised to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion and completed in the 7 days following Baseline 2 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.
  - Olanzapine: 10 mg/day for the first 3 days; 5 mg/day for the 4 subsequent days, encapsulated tablets, orally.
- Discontinuation of IMP will be initiated at the Primary Outcome or Withdrawal Visit for all patients, including those who withdraw from the study for any reason after week 1 of Period A or anytime during Period B 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.
  - Lu AF35700: Placebo for 7 days, encapsulated tablets, orally, once daily.

Efficacy Assessments

- Positive and Negative Syndrome Scale (PANSS)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Personal and Social Performance Scale (PSP)

Exploratory Assessments

- 4-item Negative Symptom Assessment (NSA-4)
- Subjective Well-being under Neuroleptics - short version (SWN-S)
- Medication Satisfaction Questionnaire (MSQ)
- Tolerability and Quality of Life (TOOL)
- Quality of Life Scale (QLS)
- Readiness for Work Questionnaire (WoRQ)

Pharmaco-economic Assessments

- Health Economic Assessment (HEA)

Pharmacokinetic/Pharmacodynamic/Translational Medicine Assessments

Blood samples will be collected during the study for:

- Pharmacokinetic analyses of olanzapine, risperidone, 9-OH risperidone, Lu AF35700 and Lu AF36152 (its major metabolite)
- CYP genotyping
- Exploratory biomarker research including gene expression profiling, pharmacogenetics, metabolomics/proteomics
- Analysis of blood levels of olanzapine and risperidone plus 9-OH risperidone to assess treatment adherence

Safety Assessments

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

Endpoints

- Primary endpoint:

  Symptoms of schizophrenia (primary endpoint for primary objective)
  - Change from Baseline 2 (Period B) to study Week 16 in PANSS total score

- Secondary endpoints:

  Global clinical impression (supportive of primary objective)
  - Change from Baseline 2 (Period B) to study Week 16 in CGI-S score

  Functioning (secondary objective)
  - Change from Baseline 2 (Period B) to study Week 16 in PSP total score

  Response at Week 16 (supportive of primary objective)
  - Response criteria is blinded to investigators and described in the *Clinical Study Protocol Addendum – Unmasked Information)*

- Exploratory endpoints:

  Subjective well-being/quality of life and treatment satisfaction
  - Change from Baseline 2 (Period B) to study Week 16 in SWN-S total score
  - Change from Baseline 2 (Period B) to study Week 16 in MSQ score
  - Change from Baseline 2 (Period B) to study Week 16 in TOOL score
  - Change from Baseline 2 (Period B) to study Week 16 in QLS score
  - Change from Baseline 2 (Period B) to study Week 16 in WoRQ score

  Symptoms of schizophrenia
  - Change from Baseline 2 (Period B) to study Week 16 in NSA-4 total score

- Safety endpoints:
  - Adverse events
  - Absolute values and changes from Baseline 2 in clinical safety laboratory tests, vital signs, weight, and ECG parameters
  - Potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values
  - C-SSRS categorisation
  - Changes from Baseline 2 in mSAS, AIMS, and BARS total scores

Statistical Methodology

The following analysis sets will be used to analyse and present the data:

- all-patients-treated set Period A (APTS_A) – all patients who took at least one dose of study medication during Period A (risperidone or olanzapine)
- all-patients-treated set (APTS) – all randomised patients who took at least one dose of double-blind study medication (Lu AF35700, risperidone or olanzapine) after randomisation (Period B)
- full-analysis set (FAS) – all patients in the APTS who had a valid Baseline 2 assessment and at least one valid post-baseline 2 assessment of PANSS total score
- The efficacy analyses will be based on the FAS. A significance level of 0.05 is used unless otherwise indicated. For all endpoints, the effects of the two doses of Lu AF35700 will be evaluated by testing the null hypothesis of no difference to the active control for each dose. Hochberg's procedure will be used to control for multiplicity.

Primary endpoint:

- Changes from Baseline 2 (Week 6) in total PANSS score at Weeks 7, 8, 10, 12, 14, and 16 will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. All patients in the FAS will be included with their observed data in Period B. Data retrieved at Week 16 from withdrawals will not be included in the primary analysis. The model will include the fixed, categorical effects of treatment (two doses of Lu AF35700 and active control), country, visit, treatment-by-visit interaction, Period-A-therapy (risperidone/olanzapine), Period-A-therapy-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order; first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary comparisons will be the contrasts between each dose and control at Week 16 based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between each dose and the active control based on this model will be reported with two-sided symmetric 95% confidence intervals and corresponding p-values.

Secondary endpoints:

- For CGI-S and PSP, the same methodology as that described for the primary endpoint will be used.
- The proportion of patients responding at Week 16 will be compared for each dose versus control using logistic regression with period A therapy, country and treatment as factors. The analysis will be done for observed cases without imputation as well as for the whole FAS, imputing non-response for all patients withdrawn prior to Week 16.
- Additional responder analyses using alternative cut points of the primary endpoint may be used to present the efficacy as measured by changes from Baseline 2 in total PANSS score.

Exploratory endpoints:

- For NSA-4, SWN-S, MSQ, TOOL, QLS, and WoRQ the same methodology as that described for the primary endpoint will be used to analyse changes from Baseline 2 of total scores at Weeks 10 and 16.

Sensitivity analyses for the primary endpoint:

- MMRM model as the primary analysis, including the retrieved data for withdrawals.
- Pattern-mixture models. Different delta (imputation of how much worse response those who withdraw would have compared to those who do complete the treatment period and who have the same profile up to time to withdrawal) will be applied.

Analyses of safety endpoints:

- The safety analyses will be based on the APTS.
- Adverse events, clinical safety laboratory tests, vital signs, weight/BMI, ECG parameters, and C-SSRS scores will be summarised using descriptive statistics. The changes from Baseline 2 in mSAS, AIMS and BARS scores at Weeks 10 and 16 will be analysed using an MMRM model as described for the primary endpoint.
- Patient disposition and demographics will be summarised using descriptive statistics.
- Plasma concentrations of Lu AF35700 and metabolite and CYP genotype will be summarised using descriptive statistics and may be used in population pharmacokinetic analyses (reported separately).

Sample Size Considerations

A total of n=180 patients per group is needed in Period B to have 90% power for at least one Lu AF35700 dose to show a significant improvement on change in total PANSS score over the active control, assuming

- a standard deviation (SD) of 20.
- a mean improvement in total PANSS score of 5.25 and 7 for the 2 doses (standardised effect size 0.26 and 0.35)
- use of Hochberg's procedure for multiplicity adjustment at 5% level of significance.

Assuming further an information loss of ~20% due to dropout in Period B, n=225 (=180/0.8) must be randomised, a total of 675 patients.

With an attrition rate of ~30% in Period A, approximately 964 (=675/0.7) patients is expected to be enrolled to meet the target of randomising 675 patients in Period B.

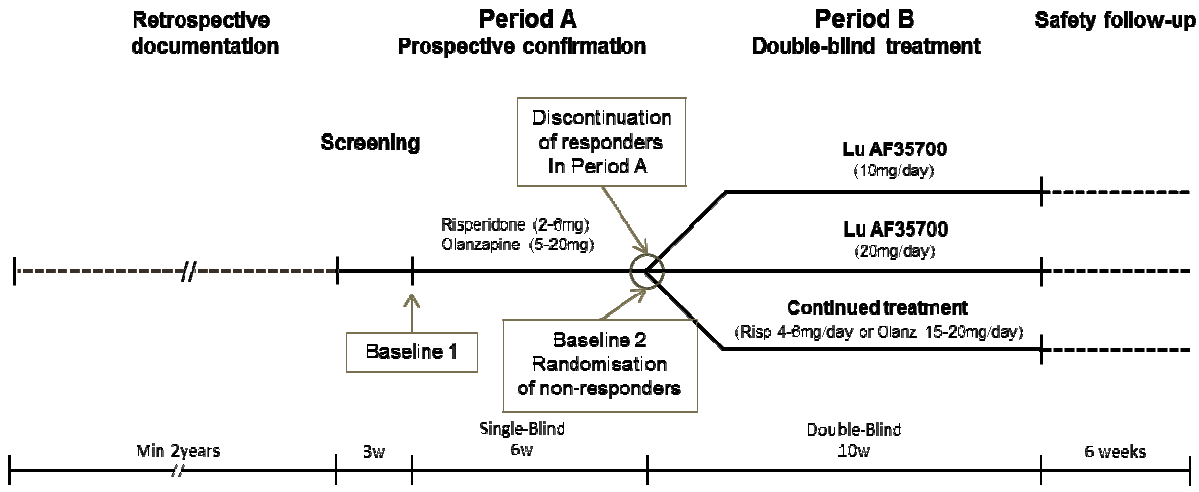
A blinded re-assessment of sample size will be considered if the blinded SD estimate or the dropout rate deviates from the assumptions. This re-assessment will be performed when 50% of the patients have completed the treatment period. A maximum of 300 randomised patients per treatment arm will be allowed in the study. The pooled standard deviation will be estimated from the Covariance Parameter Estimates from an MMRM model identical to the one to be used for the primary analysis, except without the effect of treatment, i.e. the following:

The model will include the fixed, categorical effects of country, visit, Period-A-therapy (risperidone/olanzapine), Period-A-therapy-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors.

Ethical Rationale for Study and Study Design

- Identification of novel antipsychotic agents that can effectively treat patients with schizophrenia who have failed to respond to antipsychotic therapies represents a great unmet clinical need. Per definition, these patients are highly symptomatic with associated low level of functioning and require extensive periods of hospital care, which contributes disproportionally to the overall cost of treating schizophrenia.
- Given the unique receptor binding profile of Lu AF35700 characterised by a high affinity to dopamine D1 and serotonin 5-HT6 receptors combined with a low level of dopamine D2 interaction, it is believed that Lu AF35700 can offer an effective alternative treatment option for patients with treatment-resistant schizophrenia.
- Based on data from the ongoing Phase I programme in patients with schizophrenia, the doses used in the current study is considered to be safe and well tolerated.
- The current study is a Phase III study included in the Lu AF35700 clinical development programme with the aim of generating evidence for efficacy and safety in patients with treatment-resistant schizophrenia. The design of the current study is in accordance with the Declaration of Helsinki (Ethical principles for medical research involving human subjects) as well as the EMA guideline on clinical investigation of medicinal products for treatment-resistant schizophrenia.
- In the current study, eligible patients who have had a recent treatment failure will enter a single-blind treatment period and initiate a treatment trial with either risperidone or olanzapine (two well-known and widely used antipsychotic agents), to confirm treatment resistance. Only patients where treatment resistance is confirmed will be randomised to double-blind treatment with either Lu AF35700 or to continued treatment (risperidone or olanzapine) for a period of 10 weeks. Patients who respond the initial treatment with risperidone or olanzapine will be excluded from the study. Thus, approximately one third of the confirmed treatment-resistant patients will be randomised back to the failed treatment used in the initial period of the current study. Such study design is considered ethically justifiable given the limited treatment options for this patient population.
- The duration of the double-blind treatment period in the current study is 10 weeks in order to provide sufficient time to determine the extent of attainable symptom reduction and allow safety evaluation. Enrolled patients will be asked to visit the site regularly where the investigator will evaluate the treatment outcome and decide whether it is in the patients' best interest to continue in the study. Also, patients 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. All patients enrolled in the current study will be scheduled for a Safety Follow-up Visit at the clinic 6 weeks after last dose of IMP.
- Blood samples for exploratory biomarkers will be collected in an attempt to increase the understanding of the properties of Lu AF35700, aetiology of schizophrenia, and the molecular basis of drug response.

Panel 1 Study Design



Panel 2 Study Procedures and Assessments

				Period A				Period B							
Visit	**Informed consent[a]**	**Screening[b]**	**Baseline 1**				**Baseline 2**						**Primary Outcome or Withdrawal[c]**	**Safety Follow-Up[d]**	**Efficacy Follow-up[e]**
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
End of Week		**-**	**0**	**1**	**2**	**4**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**22**	**16**
Day		**-21**	**0**	**7**	**14**	**28**	**42**	**49**	**56**	**70**	**84**	**98**	**112**	**154**	**112**
Visit Window (days)[f]		**± 7**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+3**	**± 3**
Signed informed consent	√														
Screening/Baseline Procedures and Assessments															
Diagnosis (DSM-5™)		√													
MINI-Schz		√													
Relevant social, medical and psychiatric history		√													
Demographics (age, sex, race)[g]		√													
Height		√													
Disallowed medication washout			√												
Inclusion /exclusion criteria		√	√												
Blood levels of risperidone plus 9-OH risperidone and olanzapine						√									
Inclusion criteria Period B							√								
Blood sampling for CYP2D6 and CYP2C19 genotyping							√								
Randomisation							√								
Efficacy Assessments															
PANSS		√	√	√	√	√	√	√	√	√	√	√	√		√
CGI-S		√	√	√	√	√	√	√	√	√	√	√	√		√
PSP		√	√				√			√			√		
Exploratory Assessments															

				Period A				Period B							
Visit	**Informed consent[a]**	**Screening[b]**	**Baseline 1**				**Baseline 2**						**Primary Outcome or Withdrawal[c]**	**Safety Follow-Up[d]**	**Efficacy Follow-up[e]**
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
End of Week		**-**	**0**	**1**	**2**	**4**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**22**	**16**
Day		**-21**	**0**	**7**	**14**	**28**	**42**	**49**	**56**	**70**	**84**	**98**	**112**	**154**	**112**
Visit Window (days)[f]		**± 7**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+3**	**± 3**
NSA-4			√				√			√			√		
SWN-S			√				√			√			√		
TooL			√				√			√			√		
MSQ			√				√			√			√		
QLS			√				√			√			√		
WoRQ			√				√			√			√		
Pharmaco-economic Assessments															
HEA			√				√						√		
Pharmacokinetic Assessments															
Blood sampling for olanzapine/risperidone and Lu AF35700 assays[h]									√	√			√		
Translational Medicine Assessments															
Blood sampling for gene expression profiling (RNA)[i]			√				√						√		
Blood sampling for metabolomics/proteomics (plasma)[i]			√				√						√		
Blood sampling for pharmacogenetics (optional)[j]			√												
Safety Assessments															
Adverse events[k]		√	√	√	√	√	√	√	√	√	√	√	√	√[l]	√[l]
Blood and urine sampling for clinical safety laboratory tests (fasting)		√			√		√		√	√			√	√[m]	
Serum prolactin[n]			√				√						√		
HBA1c (fasting)		√					√						√		

				Period A				Period B							
Visit	**Informed consent[a]**	**Screening[b]**	**Baseline 1**				**Baseline 2**						**Primary Outcome or Withdrawal[c]**	**Safety Follow-Up[d]**	**Efficacy Follow-up[e]**
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
End of Week		**-**	**0**	**1**	**2**	**4**	**6**	**7**	**8**	**10**	**12**	**14**	**16**	**22**	**16**
Day		**-21**	**0**	**7**	**14**	**28**	**42**	**49**	**56**	**70**	**84**	**98**	**112**	**154**	**112**
Visit Window (days)[f]		**± 7**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**+3**	**± 3**
Blood lipid profile (fasting)		√					√						√		
Vital signs		√	√	√	√	√	√	√	√	√	√	√	√		
ECGs		√					√		√	√			√		
Body weight		√	√				√						√		
Waist circumference			√				√						√		
Physical Examination			√										√		
Movement rating scales (AIMS, BARS, mSAS)			√				√			√			√		
C-SSRS		√	√	√	√	√	√	√	√	√	√	√	√	√	
Other Study Procedures															
IMP dispensed			√	√	√	√	√	√	√	√	√	√	√[o]		
Possible change in IMP[p]					√	√									
IMP returned and accountability				√	√	√	√	√	√	√	√	√	√	√	
Recent and concomitant medication		√	√	√	√	√	√	√	√	√	√	√	√	√	√
Urine drug screen[q]		√				√									
Pregnancy test[p]		√											√		
Urine pregnancy test[r]							√[r]								

a *Informed Consent Form* must be signed before any study-related procedures are initiated, including washout of disallowed medications. If wash-out is needed, the ICF will be signed before wash-out is initiated and before the Screening Visit.

b The Screening Visit assessments may be extended over several days if needed. The date of the first assessment should be entered in eCRF as the Visit Date.

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

d Safety Follow-up Visit must be conducted as a visit to the clinic. The visit should be planned 6 weeks after last dose of IMP. 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 eCRF). A Safety Follow-up Visit will not be performed for patients who continue in the extension study.

e This visit is only for patients that withdraw from Period B of the study before the scheduled Primary Outcome Visit (Week 16). Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will be asked to attend an Efficacy Follow-up visit at the date of their last scheduled visit of Period B (study Week 16) for the assessment of efficacy, safety and concomitant medication.

f 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 1 Visit.

g The patient's demographics information (age, sex, race) is to be recorded in the eCRF at informed consent signature date.

h The blood samples for Lu AF35700 (IMP), Lu AF36152 (metabolite), olanzapine, risperidone, and 9-OH risperidone analysis will be drawn as close to the ECG recordings as possible.

i Exploratory gene expression profiling (RNA) and metabolomics/proteomics are an integrated part of the study and are covered by the main Patient Information Sheet.

j Sampling for pharmacogenetics is optional and a separate Patient Information Sheet covers this analysis. This sampling should preferably be at the Baseline 1 Visit, but may be collected at any visit that includes a clinical safety laboratory sample.

k Signs and symptoms present at Screening and/or Baseline 1 (before IMP intake) must be recorded on an *Adverse Event Form*.

l Only for adverse events ongoing at Primary Outcome/Withdrawal Visit and new SAEs.

m Only to be taken if the laboratory test was clinically significantly abnormal at the Primary Outcome/Withdrawal Visit.

n Results will remain blinded throughout the study.

o One week supply will be provided for down-titration of blinded IMP.

p The dose of IMP can be increased for efficacy or decreased for tolerability at scheduled or unscheduled visits between weeks 2 and 4.

q Urine drug screen tests can be repeated any time during the study at the discretion of the investigator.

r S-βhCG pregnancy test should be performed at the Screening and the Primary Outcome/Withdrawal Visit for women of childbearing potential. Urine pregnancy test should be performed at Baseline 2 Visit and can be performed any time during the study at the discretion of the investigator. Any positive urine pregnancy test must be confirmed by a S-βhCG pregnancy test.

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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
BMI	Body Mass Index
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 organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 isoenzyme
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EPS	extra pyramidal symptoms
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FDA	United States Food and Drug Administration
GPV	Division of Global Pharmacovigilance, H. Lundbeck A/S
HBA1c	glycated hemoglobin, 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
LLOQ	lower limit of quantification
Lu	Lundbeck
MAD	multiple ascending dose
MINI-Schz	Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders
MMRM	mixed model for repeated measurements
mRNA	messenger ribonucleic acid
mSAS	Simpson Angus Scale
MSQ	Medication Satisfaction Questionnaire
NOAEL	no-observed-adverse-effect level
NSA-4	4-item Negative Symptom Assessment
PANSS	Positive and Negative Syndrome Scale
PCR	polymerase chain reaction
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
popPK	population pharmacokinetic(s)
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
qPCR	quantitative polymerase chain reaction
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
REML	restricted maximum likelihood
RNA	ribonucleic acid
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
SUSAR	suspected unexpected serious adverse reaction
SWN-S	Subjective Well-being under Neuroleptics – short version
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 1.1.5 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

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.

In human hepatocytes, the major metabolite was the N-desmethyl metabolite (Lu AF36152). Other metabolites included two mono-hydroxy metabolites, a possible O-methyl catechol metabolite, two dihydrodiols, and two mono-hydroxy metabolites of Lu AF36152.

At the predicted therapeutic plasma concentrations of Lu AF35700 and Lu AF36152, the drug-drug interaction (DDI) potential due to CYP inhibition or CYP induction appears to be low. As the CYP2D6 and CYP3A4/5 are the major CYP enzymes responsible for the overall metabolism of Lu AF35700, strong inhibitors of these enzymes or CYP2D6 poor metaboliser status may result in elevated plasma concentrations.

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 in 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 study is a Phase III study included in the Lu AF35700 clinical development programme and will be conducted in order to establish the appropriate clinical effective dose range of two fixed doses of Lu AF35700 as a potential treatment of treatment-resistant schizophrenia (TRS).

Clinical studies present an excellent opportunity for collecting large numbers of biological samples from well-characterised patient populations for research on the aetiology of schizophrenia and the molecular basis of the drug response (intended or adverse). Thus, samples will be collected for exploratory biomarker analyses to investigate associations between biological parameters, for example, genetic variants, mRNA concentrations, protein or endogenous metabolite concentrations and clinical features such as disease symptoms, drug response, and potential adverse events.

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 efficacy of 10 and 20 mg/day of Lu AF35700 on schizophrenia symptoms in patients with TRS

Secondary Objective

- To evaluate the efficacy of 10 and 20 mg/day of Lu AF35700 on functioning of patients with TRS

Exploratory Objective(s)

- To explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on quality of life

- To explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on treatment satisfaction
- To explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on tolerability
- To explore the efficacy of 10 and 20 mg/day of Lu AF35700 in patients with TRS on negative symptoms

Safety Objective

- To evaluate the safety and tolerability of 10 and 20 mg/day of Lu AF35700 in patients with TRS

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[7]

This is an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, active-controlled, fixed-dose study.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[8] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

The total study duration per patient from Screening to the end of Follow-Up will be approximately 25 weeks. The study will consist of 4 Periods:

- Screening Period (3 weeks)
- Period A – Prospective Confirmation Period (6 weeks)
- Period B – Double-blind Treatment Period (10 weeks)
- Safety Follow-Up Period (6 weeks)

Approximately 675 patients (225 patients per group) are planned to be randomised in Period B.

Patients will enter a Screening Period of up to 21 days to assess eligibility.

Non-acute male and female patients, aged ≥18 years, with a primary diagnosis of schizophrenia according to the DSM-5™ who meet criteria of treatment resistance will be screened for eligibility. Eligible patients will be documented to have failed to show an adequate response in their level of antipsychotic symptoms despite at least one treatment with an adequate dose of one or more antipsychotic medication(s) for at least 6 weeks during the last 2 years prior to Screening.

Patients should be treated with adequate dose(s) and agent(s) of antipsychotic treatment for at least 2 weeks prior to Screening. Current antipsychotic medication will be down-tapered within the first 7 days of Period A according to Appendix II.

130 sites are planned in approximately 18 countries (in-/outpatient clinics).

Patients, who meet the pre-specified selection criteria, will enter a single-blinded 6-week treatment period (Period A) with risperidone,[9] or olanzapine[10] if they are currently treated with risperidone or 9-OH-risperidone (Invega™), to prospectively confirm their resistance to antipsychotic treatment. Patients who do not fulfil the inclusion criteria for Period B will be withdrawn from the study. Current antipsychotic medication will be down-tapered within the first 7 days of Period A as described in section 6.1.

Patients who fulfil the inclusion criteria for lack of clinically relevant improvement during Period A will be considered treatment-resistant and enter the double-blind treatment period (Period B). The specific inclusion criteria for Period B will be blinded to the investigators. At Baseline 2, patients will be randomly assigned (1:1:1) to 10 weeks of double-blind treatment with either Lu AF35700 10 mg/day, Lu AF35700 20 mg/day or to continue the treatment allocated in Period A (risperidone or olanzapine). The randomisation will be stratified by country and Period A therapy.

All patients, including patients with a clinically relevant improvement, patients who have completed the treatment period and those who withdraw, will be scheduled for a Safety Follow-up Visit at the clinic for safety assessments 42 days after the last dose of IMP. Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will be asked to attend an Efficacy Follow-up Visit at the date of their last scheduled visit of Period B (Week 16) for the assessment of efficacy, safety and concomitant medication.

An internal Safety Committee at H. Lundbeck A/S has been established for Lu AF35700 and the committee will perform regular evaluations of blinded 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 randomised, double-blind, active-controlled, fixed dose design of the study aims to evaluate the safety and efficacy of two doses of Lu AF35700 in patients with TRS. The treatment-resistant criteria used in this study are failure to respond after two trials of antipsychotic medication of adequate dose and duration of at least 6 weeks.[11] The first failed antipsychotic trial will be retrospectively documented as persistent positive symptoms and the current presence of at least moderately severe illness at study inclusion as defined by Inclusion Criteria 9 and 10, as well as persistent illness and drug-refractory condition as defined by Inclusion Criterion 8. Patients that meet the above criteria and have been treated for at least 2 weeks[12] with an adequate dose of antipsychotic will enter a single blinded antipsychotic trial (Period A) of 6 weeks duration in which they will be treated with

risperidone, or olanzapine if patients were currently treated with risperidone. The rationale for considering two failed trials as sufficient evidence of TRS is supported by the finding that subjects not responding to two adequate antipsychotic trials have less than 7% chance of responding to another trial;[13] a criterion which has been broadly adapted in recent TRS studies.[14]

Patients that fail the treatment assigned during Period A, the criteria of which will be blinded to the investigator, will be randomised to continue treatment with risperidone or olanzapine or to treatment with one of two fixed doses of Lu AF35700. The rationale for the choice of risperidone or olanzapine for the prospective antipsychotic trial is their well-established efficacy and effectiveness in drug-responsive patients with schizophrenia; which will enable a clear differentiation between responders and non-responders, and thus are an appropriate comparator for Lu AF35700 during Period B. In order to rule out lack of treatment adherence as one of the possible reasons for treatment failure, blood levels of risperidone plus 9-OH-risperidone, and olanzapine will be assessed in Period A.[15,16] The blinding of the investigators to the randomisation criteria at the end of Period A is designed to further reduce possible sources of bias in the assessment of efficacy in TRS patients.

In this study, patients withdrawing during Period B (except those withdrawing due to withdrawal of consent) will be asked to attend an Efficacy Follow-up Visit, in order to achieve a complete as possible dataset from these patients and thereby minimising bias. The primary analysis assumes data are missing at random. As sensitivity analysis, this assumption will be investigated by utilising the retrieved dropout data from the Efficacy Follow-up visit.

The doses of risperidone and olanzapine used in this study are known according to be safe, effective and well-tolerated.[17] The 10 and 20 mg doses 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 D_2 receptor occupancy in healthy volunteers (see *Investigator's Brochure).*[4] The treatment duration of 10 weeks was chosen as an adequate time period necessary to achieve steady-state of the plasma levels of Lu AF35700 and its active metabolite (Lu AF36152) given their long half-lives and to provide sufficient time to determine the extent of attainable symptom reduction and allow safety evaluation.[4] The primary efficacy endpoint will be based on the PANSS[18] a well established scale for assessing severity of the symptoms of schizophrenia. The CGI-S[19,20] will be used as a secondary efficacy measure to assess clinical response. The exploratory assessment of the severity of the negative symptoms of schizophrenia will be done using the NSA-4.[21]

Improvement in functional outcome and quality of life are important treatment goals in the management of patients with schizophrenia. In the current study, effects on functional outcomes will be assessed using the PSP.[22]

Taking into account the substantial health economic burden of TRS, it is also necessary to evaluate the effect of the Lu AF35700 on subjective well-being/quality of life, treatment satisfaction, disability and health care resource utilisation. These will be assessed in the study through clinician-reported outcomes such as QLS[23]and WoRQ[24] , as well as, patient reported outcomes such as SWN-S[25], MSQ[26], TooL[27] and HEA.

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.[28] The primary variables for assessing those parameters include body weight/BMI, waist circumference, fasting blood glucose, glycosylated haemoglobin [HbA1c] and lipids (triglycerides, total cholesterol, low-density lipoprotein [LDL], and high density lipoprotein [HDL] cholesterol).

4 Ethics

4.1 Ethical Rationale

A subgroup of patients with schizophrenia show persistent positive psychotic symptoms, at least moderately severe and persistent illness, and are considered drug-refractory. Such patients constitute between 10 and 60% of the total patient population, depending on the criteria used to assess TRS.[29,30]

Identification of novel antipsychotic agents that can effectively treat patients with schizophrenia, who have failed to respond to antipsychotic therapies represents a great unmet clinical need. Per definition, these patients are highly symptomatic with associated low level of functioning and require extensive periods of hospital care which contributes disproportionally to the overall cost of treating schizophrenia.

Given the unique receptor binding profile of Lu AF35700 characterised by a high affinity to dopamine D_1 and serotonin 5 HT6 receptors combined with a low level of dopamine D_2 interaction, it is believed that Lu AF35700 can offer an effective alternative treatment option for patients with TRS.

The design of the current study is in accordance with the *Declaration of Helsinki*[7] (Ethical principles for medical research involving human subjects) as well as the EMA guideline on clinical investigation of medicinal products for treatment-resistant schizophrenia.[31]

In the current study, eligible patients who have had a recent treatment failure will enter a single-blind treatment period and initiate a treatment trial with either risperidone or olanzapine (two well-known and widely used antipsychotic agents) to confirm treatment resistance. Only patients where treatment resistance is confirmed will be randomised to double-blind treatment with either Lu AF35700 or to continued treatment (risperidone or olanzapine) for a period of 10 weeks. Patients who respond the initial treatment with risperidone or olanzapine will be excluded from the study. Thus, approximately one third of the confirmed treatment-resistant patients will be randomised back to the failed treatment used in the initial period of the current study. Such study design is considered ethically justifiable given the limited treatment options for this patient population.

The duration of the double-blind treatment period in the current study is 10 weeks in order to provide sufficient time to determine the extent of attainable symptom reduction and allow safety evaluation. Enrolled patients will be asked to visit the site regularly, where the investigator will evaluate the treatment outcome and decide whether it is in the patients' best interest to continue in the study. Also, 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. All patients enrolled in the current study will be scheduled for a Safety Follow-up Visit at the clinic 6 weeks after last dose of IMP. Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will be asked to attend an Efficacy Follow-up Visit at the date of their last scheduled visit of Period B (study Week 16) for the assessment of efficacy, safety and concomitant medication.

In accordance with *Good Clinical Practice*,[8] 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*,[8] the investigator will be responsible for all study-related medical decisions.

4.2 Informed Consent

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

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) and informant/caregiver (if applicable

per local requirements) the aims, methods, and potential hazards of the study and any discomfort it may entail. The patients and their legal representatives (if applicable) and informant/caregiver (if applicable per local requirements) 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) and informant/caregiver (if applicable per local requirements) must be informed of the possibility of withdrawing consent (section 8.3).

The patients and their legal representatives (if applicable) and informant/caregiver (if applicable per local requirements) 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) and informant/caregiver (if applicable per local requirements). 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 informant/caregiver (if applicable per local requirements) and signed and dated by the investigator or a designee. The patients and their legal representatives (if applicable) and informant/caregiver (if applicable per local requirements) 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.

The blood samples for exploratory biomarker analysis may be shared with academic or public institutions; 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.

4.3 Personal Data Protection

In accordance with *European Union Directive 95/46/EC*,[32] 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,*[32] and country-specific guidelines and laws.

4.4 Independent Ethics Committees (IECs) and Institutional Review Boards) (IRBs)

The Contract Research Organisation (CRO) will be responsible for submission of the protocol (blinded protocol and *Clinical Study Protocol Addendum - Unmasked Information)* and other appropriate documents to the IECs/IRBs. The blinding of the investigator should be ensured and any correspondence to and from the IECc /IRBs should be sent via the CRO. Members of the IECs/IRBs will be requested not to communicate directly with the investigators on the unblinded design of the study.

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 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 (blinded protocol and *Clinical Study Protocol Addendum - Unmasked Information*) 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 randomised:	675
to complete the treatment period:	540

Approximately planned number of:

study sites:	130

5.2 Patient Recruitment

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

The sponsor reserves the right to utilize quality oversight methods to determine appropriateness of continued patient screening at a given site.

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

5.3 Selection Criteria

Patient selection 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

1. The patient is capable of communicating with the site personnel.
2. The patient and his or her legal representative (if applicable) is/are able to read and understand the Informed Consent Form.
3. The patient and his or her legal representative (if applicable) has/have signed the Informed Consent Form.
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™ and confirmed by the MINI-Schz.
7. The patient has been treated with adequate dose(s) and agent(s) of antipsychotic treatment for at least 2 weeks prior to Screening (see chapter 12).
8. The patient has failed to show an adequate response in the level of psychotic symptoms despite at least one documented treatment trial with an adequate dose of an antipsychotic agent prescribed for an adequate time (at least lasting for 6 weeks) during 2 years prior to Screening (see chapter 12). The failure to respond to the current antipsychotic treatment trial may be considered a retrospective failed treatment, if the patient was treated for 6 weeks with adequate dose(s) and agent(s).
9. The patient has a PANSS total score of ≥80 and a score of ≥4 on at least 2 of the following PANSS items (at Screening and at the first visit of Period A [Baseline 1]):
   - P2 - Conceptual disorganization
   - P3 - Hallucinatory behaviour
   - P6 - Suspiciousness/persecution

- G9 - Unusual thought content

10. The patient has a CGI-S score of ≥4 at Screening and at the first visit of Period A (Baseline 1).
11. The patient is a man or woman, aged ≥18 years.
12. 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.
13. 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).
14. 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); the contraception must be used from the Screening Visit to ≥3 months after the last dose of IMP, 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
15. 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 Screening Visit

Inclusion criteria Period B

The inclusion criteria will be blinded to investigators. The inclusion criteria for Period B are described in the *Clinical Study Protocol Addendum - Unmasked Information*.

Exclusion Criteria

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 primary psychiatric disorder other than schizophrenia, as assessed using the MINI-Schz.
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 an acute exacerbation of his/her psychotic symptoms according to the investigator's judgement.
13. The patient has experienced a symptom relief corresponding to a CGI-Severity rating of 3 (mild) or less as a result of antipsychotic treatment during the majority of time in the 2 year period prior to Screening.
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 judgement, or who answers on the C-SSRS:
    - "Yes" to questions 4 or 5 on the Suicidal Ideation section within the last 3 months at Screening, OR
    - "Yes" to any question on the Suicidal Behaviour section within the last 3 months at Screening, OR
    - "Yes" to questions 4 or 5 on the on the Suicidal Ideation section at Baseline 1
16. 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.
17. The patient has had neuroleptic malignant syndrome.
18. The patient has been treated with, AND is resistant to, clozapine according to the investigator's judgement.

Medical

19. The patient has any other disorder for which the treatment takes priority over treatment of schizophrenia or is likely to interfere with study treatment or impair treatment compliance.
20. 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.
21. 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).
22. 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
    - endocrinological 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
23. The patient has clinically significant abnormal vital signs at the Screening Visit.
24. 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
25. The patient meets ANY of the following criteria:
    - HbA1C >8%, OR

- experiencing severe hypoglycaemia (per American Diabetic Association criteria)[33] AND/OR has been hospitalised for ketoacidosis – both within the last 12 months, OR
- diabetes or diabetes treatment which is not considered stable according to the investigator

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 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)
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 8.3 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 attempts have been made to contact the patient]).

A patient must be withdrawn from treatment if:

- the investigator considers it, for safety and/or study compliance reasons, in the best interests of the patient that he or she be withdrawn
- any personnel breaks the randomisation code for that patient
- 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 QT_{cF} interval >500 ms or a change from Screening in the QT_{cF} interval >60 ms concurrently with a QT_{cF} 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 did not take IMP for at least 6 consecutive days
- 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

Patients, who meet the pre-specified selection criteria (including the criteria for treatment resistance), will enter a single (patient)-blinded treatment period with risperidone[9] or olanzapine[10] to confirm their resistance to antipsychotic treatment at Baseline 1. Patients will be initiated on risperidone 2 mg/day and up-titrated to 6 mg/day by the end of the first week, except if they have failed on risperidone (or 9-OH-risperidone; Invega™) in the most recent treatment trial, in which case patients will be initiated on olanzapine at 5 mg/day and up-titrated to 15 mg/day by the end of the first week. Current antipsychotic medication will be down-tapered within the first 7 days of this treatment period. Patients will be up-titrated according to the following scheme:

- Risperidone: 2 mg/day for the first 2 days; 4 mg/day for the next 2 days; 6 mg/day for the last 3 days

- Olanzapine: 5 mg/day for the first 2 days; 10 mg/day for the next 2 days; 15 mg/day for the last 3 days

In the subsequent week patients will receive either risperidone 6 mg/day or olanzapine 15 mg/day and thereafter either risperidone 4 or 6 mg/day or olanzapine 15 or 20 mg/day for the subsequent four weeks, which can be increased for efficacy or decreased for tolerability between weeks 2 and 4, according to the investigator's clinical judgement. Patients will be treated with at least 6 mg/day of risperidone (or with 4 mg/day in case the dose of 6 mg was not tolerated and had to be reduced) or with at least 15 mg/day of olanzapine for the last 2 weeks. Patients currently treated with 'depot' antipsychotic medications can, after signing the ICF, be down-tapered by skipping one full treatment cycle plus 3 days before Baseline 1. Patients who do not fulfil the inclusion criteria for Period B will be withdrawn from the study. If the patient is withdrawn during Period A, the investigator will have the option to continue the patient on the treatment assigned during Period A, as prescribed by the investigator, or discontinue IMP.

Patients who fulfil the inclusion criteria for lack of clinically relevant improvement during Period A will be considered treatment-resistant and enter the double-blind treatment period (Period B) at Baseline 2. The specific inclusion criteria for Period B will be blinded to the investigators. Patients will be randomly assigned (1:1:1) to 10 weeks of double-blind treatment with either Lu AF35700 10 mg/day, Lu AF35700 20 mg/day, or to continue the

treatment allocated in Period A at the dose set at last visit of Period A (Week 4). The randomisation will be stratified by country and Period A therapy (risperidone or olanzapine). No dose adjustments will be allowed during Period B. Patients randomised to Lu AF35700 will be initiated on Lu AF35700 10 mg/day without titration or 20 mg/day starting with 10 mg for 4 days followed by 20 mg/day thereafter. For the patients randomised to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion and completed in the 7 days following Baseline 2 according to the following scheme:

- Risperidone: 4 mg/day for the first 3 days; 2 mg/day for the 4 subsequent days
- Olanzapine: 10 mg/day for the first 3 days; 5 mg/day for the 4 subsequent days

At the Primary Outcome or Withdrawal Visit for all patients, including those who withdraw from the study for any reason after Week 1 of Period A or anytime during Period B, discontinuation of IMP will be initiated according to the following scheme:

- Risperidone: 4 mg/day for the first 3 days; 2 mg/day for the 4 subsequent days
- Olanzapine: 10 mg/day for the first 3 days; 5 mg/day for the 4 subsequent days
- Lu AF35700: Placebo for 7 days

In order to reduce biases associated with changes in treatment between the study periods and for blinding purposes during the down titration of risperidone or olanzapine, patients will be given two identical capsules per day throughout all treatment periods.

The patients will be instructed to take 2 capsules, for oral use, together in the morning or evening. The capsules are to be swallowed whole.

At Visit 2 (Baseline 1), the first dose is to be taken the day after study medication has been dispensed to the patient.

For patients taking IMP in the morning, on scheduled visit days, they should not take IMP in the morning prior to the visit. IMP should be taken from the new wallet card dispensed the day of the visit, after all blood samples have been taken as part of the visit procedures.

For patients taking IMP in the evening, on scheduled visit days, patients will take their IMP from the new wallet card dispensed the day of the visit.

For tolerability reasons, the investigator may decide to switch the patient's dosing schedule from evening to morning OR morning to evening. If the patient switches at a specific visit, then it is acceptable to skip one dose of IMP.

All wallet cards should be returned at the next study visit for new wallet cards to be dispensed to the patient.

IMPs, Formulations, and Strengths

The IMPs supplied by Lundbeck in this study are:

- Lu AF35700 - encapsulated tablets in strengths of 10 and 20 mg
- Risperidone - encapsulated tablets in strengths of 2 and 4 mg

- Olanzapine - encapsulated tablets in strengths of 5, 10 and 15 mg
- Placebo - encapsulated tablets

The IMPs will be identical in appearance.

6.2 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 containing 20 capsules.

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.

6.3 Method of Assigning Patients to Treatment

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

An Interactive Voice Response System (IVRS) will be used in this study. When a patient is to be randomised, the investigator will contact the IVRS. The IVRS will allocate the patient to a treatment group during the call and assign the patient a randomisation number in accordance with the specifications from the Department of Biostatistics, H. Lundbeck A/S, and then follow up by fax, e-mail, or the web (depending on availability or preference at the site).

6.4 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 Lundbeck)
- 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.

6.5 Unblinding Procedures

Division of Global Pharmacoviligance (GPV), and the investigator or the pharmacist (if applicable) will have access to the details of the double-blind treatment for each patient. Access to these details will be via IVRS.

The IVRS unblinding procedure is described in the *IVRS User Guide*.

The investigator may only break the code if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator must consult the CRA before breaking the code. The investigator must record the date, time, and reason for breaking the code on the *IMP Code Break Form* (this corresponds to the Primary Outcome/Withdrawal Visit, as the patient must be immediately withdrawn from the study) and sign the form. If the emergency situation was an adverse event, it must be recorded on an *Adverse Event Form*. The CRA must be notified immediately.

The IVRS will also capture the date and time of the code break call. Information on the allocated treatment will be provided during the call and by fax or e-mail, depending on availability/preference.

6.6 Post-study Access to IMP(s)

Patients who completed treatment of Period B (Visit 12) may continue into the optional 52-weeks open-label extension study 16159B, if informed consent has been obtained and if eligible as judged by the investigator. For patients who do not continue into the extension study, the patient should be treated according to the current clinical practise at the discretion of the investigator.

7 Concomitant Medication

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

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 <3 months prior to the Screening Visit 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.

The use of potent CYP2D6 and CYP1A2 inhibitors and CYP3A4 inducers is not permitted during the study, as they may affect the pharmacokinetic properties of risperidone or olanzapine in a manner that would require dose adjustment.[9,10] Examples of inhibitors and inducers are provided in Appendix II.

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)

Informed consent must be obtained before any study-related procedures are initiated, including washout of disallowed medications. After informed consent is obtained, down tapering of depot antipsychotic medications and washout of disallowed medications begins, if applicable, and must comply with the requirements listed in Appendix II. The screening period begins at the Screening Visit. Screening evaluations are described in Panel 2.

The Screening Visit assessments may be extended over several days if needed. The date of the first assessment should be entered in eCRF as the Visit Date.

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 enrollment and data quality. Sites should submit specific screening information within 72 hours from the Screening Visit for review by external medical team or sponsor prior to proceeding to Baseline 1.

Decisions regarding inclusion of patients and assessment of patient safety throughout the trial 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.

Please refer to chapter 12 for requirements for documentation and medical records for patients to be enrolled.

8.2.1 Pre-screening

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 Outpatient Hospitalisation

Transient outpatient hospitalisation of up to 5 days duration, which according to the investigator judgement might benefit a patient in the course of the study, must be approved in advance by the study's Medical Expert. Such hospitalisations might be extended up to a maximum of two additional periods of 3 days with approval of the Medical Expert. The number hospitalisation days of patients during the study will be captured at every visit in the eCRF.

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 13)

The safety follow-up is conducted to capture serious adverse events (SAEs) events 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 approximately 42 days after last dose of IMP as 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.

No Safety Follow-up Visit is to be performed for patients who continue in the extension study.

8.6 Efficacy Follow-up Visit (Visit 14)

Patients withdrawn during Period B will be asked to attend an efficacy follow-up visit at the time of their scheduled Primary Outcome Visit (study Week 16), 10 weeks (±3 days) after Baseline 2 (study Visit 6), except for those who withdraw their consent. This follow-up will include safety, concomitant medication and selected efficacy assessments.

8.7 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 Informed Consent Date

Informed consent signature date and patient's demographics information (age, sex, race) is to be recorded in the eCRF after obtaining of the signed informed consent.

9.1.2 Other Baseline Characteristics

At the screening visit, the following will be recorded or assessed:

- Diagnosis (DSM-5™)
- Relevant medical and psychiatric history – including retrospective documentation of treatment failure
- Height and weight
- Prior antipsychotic and disallowed medication washout

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

9.1.3 Diagnostic and Screening assessments

9.1.3.1 Mini International Neuropsychiatric Interview for Schizophrenia and Psychotic Disorders Studies (MINI-Schz)

The MINI-Schz (version 7.0.1)[34] is a structured diagnostic interview designed to provide a brief standardised evaluation of major Axis I psychiatric disorders in DSM-5. Each of the 17 independent diagnostic modules consists of screening and a series of secondary questions to be answered with “yes” or “no” responses. If the patient answers “no” to a screening question,

the clinician starts asking questions from the next module. A clinician can use the MINI-Schz after a short training session. It takes approximately 20 minutes to administer the MINI-Schz.

The MINI-Schz will be administered in the local language. 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 MINI-Schz will be provided to the site.

9.1.3.2 Rater Qualification and Certification for MINI-Schz

The MINI-Schz must only be administrated by clinicians having experience with structured interviews in patients with schizophrenia. Any exceptions must be discussed and approved by Lundbeck.

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.

A MINI-Schz training session will be organised prior to the start of the study. Documentation of rater training and certification will be delivered to raters for archiving in the I-TMF. No patient must be rated before the documentation has been delivered. New raters joining the study will be trained and certified using the same certification processes.

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

9.1.4 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 Efficacy Assessments

9.2.1 Use of Assessment Tools

The following efficacy assessments will be used:

- PANSS − clinician-rated, assessing symptoms of schizophrenia
- PSP − clinician-rated, assessing personal and social performance
- CGI-S − clinician-rated, assessing global impression

The PANSS will be administered in the local language. The PSP and CGI-S 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.

9.2.1.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS[18] 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[35] (SCI–PANSS) will be used to facilitate the administration of the PANSS assessment. The structured questionnaire *PANSS Checklist* will be used to collect the PANSS informant data in a consistent manner throughout the study.

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

9.2.1.2 Personal and Social Performance Scale (PSP)

The PSP[22] 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.

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

The CGI[19,20] 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.

9.2.1.4 Rater Qualification and Certification

The PANSS and the PSP should be administrated by clinicians (see 9.1.3.2). As a pre-requisite, PANSS raters must be experienced in patients with schizophrenia and in administering the PANSS.

The CGI-S must be administered by the clinician (see 9.1.3.2) responsible for the patient.

Any exceptions must be discussed and approved by Lundbeck.

Only raters who qualify on a PANSS rater training and certification programme will be authorised to rate the PANSS for the study. Individual scores from the PANSS rater qualification session will be used to document the inter-rater reliability and filed in the Sponsor TMF.

A CGI-S and PSP training sessions will be organised prior to the start of the study.

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

New raters joining the study will be trained and certified using the same certification processes.

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.

To the extent possible, at Visit 12/Primary Outcome Visit a different rater than the one doing the rating at Visit 6 should assess the patient.

Lundbeck reserves the right to use external quality oversight methods (audio and worksheet review) may be used to verify the accuracy of the PANSS scoring. The process for scale data oversight will be outlined in a separate document. Audio monitoring and review will be performed on behalf of Lundbeck by a third party vendor. The audios will be uploaded to a server with limited and controlled access. In agreement with Lundbeck, audios will be destroyed at the end of the study.

The recording equipment will be provided by a third party vendor selected by the sponsor.

9.3 Pharmacoeconomic Assessment - Health Economic Assessment Questionnaire (HEA)

The HEA is a questionnaire aiming at monitoring patients' healthcare resource utilisation such as physicians' visits, outpatient and inpatient services, medications and relevant services.

The study personnel who conduct 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 Visit 2, and a *Follow-up Evaluation* version, which is to be used at Visit 6 and Visit 12.

It takes approximately 10 minutes to complete the HEA.

The HEA will be administered in English only. Country specific versions will be used for United States and Canada. Instructions on how to complete the questionnaire will be provided to the sites.

9.4 Pharmacokinetic Assessment

Blood samples for IMP quantification (2 mL per timepoint) will be drawn in 2mL 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 olanzapine, risperidone, 9-OH risperidone, Lu AF35700 and Lu AF36152 using analytical methods validated in accordance with the EMA *Guideline on Bioanalytical Method Validation*[36] and the FDA *Guidance for Industry*.[37]

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.

9.5 Analysis of serum levels of risperidone plus 9-OH risperidone or olanzapine

A blood sample will be drawn to analyse the serum levels of risperidone plus 9-OH risperidone or olanzapine, in accordance with Panel 2.

Approximately 3 ml blood will be collected and the sample will be analysed at a central laboratory. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

9.6 Safety Assessments

9.6.1 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.

9.6.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 3.

Panel 3 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)** [d]
B-MCHC	S-aspartate aminotransferase (AST)	U-protein (dipstick)
B-total leucocyte count	S-lactate dehydrogenase (LDH)[g]	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**[d]
B-lymphocytes (% of total leucocytes)	S-potassium	U-Amphetamines
B-monocytes (% of total leucocytes)	S-calcium (total)	U-Barbiturates
B-thrombocyte count	S-chloride	U-Benzodiazepines
P-INR (prothrombin ratio)[g]	S-bicarbonate	U-Cannabiniods
Lipids[a]		U-Cocaine
S-cholesterol (total) (fasting)	**Endocrine and Metabolic**[a]	U-Methadone
S-triglycerides (fasting)	S-albumin	U-Opiates
S-low density lipoprotein (LDL)	S-glucose (fasting)	U-Phencyclidine
S-high density lipoprotein (HDL)	S-prolactin [b]	**Pregnancy (women only)**
	B-HbA1c [c]	S-hCG
	S-total protein	Urine Dipstick[e]
		Additional Test
		S-creatine phosphokinase (CPK) [f]
B – blood; P – plasma; S – serum; U – urine		

a Clinical chemistry.

b Result will remain blinded until unblinding of the study. Test results >250 µg/L (250 ng/mL) will be reported by the central laboratory to the Medical Expert for clinical follow-up with the investigator.[38]

c Performed at the Screening, Baseline 2 and Primary Outcome/Withdrawal visit only

d Urine samples will be collected and analysed at the site using dipsticks.

e 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.

f S-troponin T, reflex for CPK >500U/L.

g Re-sampling for laboratory tests deemed not evaluable by the central laboratory will only be required for appropriate clinical follow-up due to Medical History or previous clinically relevant abnormal findings.

Blood samples for the clinical safety laboratory tests will be collected as outlined in Panel 3. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

The blood samples will be analysed at a 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.

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

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

9.6.3 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.

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

9.6.4 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. The Body Mass Index (BMI) will be calculated automatically within the eCRF using the height measurement taken at the Screening Visit and the body weight taken at Visit 1, 2, 6 and 12 according to the standard formula: weight (in kilograms) over height squared (in centimeters).

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*.

9.6.5 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 QTc 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*.

9.6.6 Physical examinations

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 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. Height is measured at the Screening Visit.

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

9.6.7 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.

9.6.7.1 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.

The C-SSRS will be provided in the local language. Only scales provided by Lundbeck that have been validated in the language to which they have been translated will be used in this study.

It takes approximately 5 minutes to administer and rate the C-SSRS.

9.6.7.2 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[39] 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.

9.6.7.3 Barnes Akathisia Scale (BARS)

The BARS[40] 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.

9.6.7.4 Modified Simpson Angus Scale (mSAS)

The mSAS[41,42] 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.

9.6.7.5 Rater Qualification and Certification

The C-SSRS should be rated by a clinician (see 9.1.3.2). 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.

C-SSRS, AIMS, BARS, and mSAS training sessions will be organised prior to the start of the study. Documentation of rater training and certification will be delivered to raters for archiving in the investigator trial master file (I-TMF). No patient must be rated before the documentation has been delivered.

New raters joining the study will be trained and certified using the same certification processes.

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

9.7 Exploratory Assessments

The following exploratory assessments will be used:

- NSA-4 – clinician rated, assessing the severity of negative symptoms of schizophrenia
- QLS – clinician-rated, assessing quality of life
- WoRQ – clinician rated, assessing readiness to work in patients with schizophrenia
- SWN-S – patient reported, assessing subjective effects of neuroleptics
- MSQ – patient reported, assessing satisfaction with medication
- TooL – patient reported, assessing impacts of side effects on quality of life

The NSA-4 and QLS will be administered in the local language. WoRQ will be administered in English only. The SWN-S, MSQ and TooL will be completed by the patient in the local language. 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.

The SWN-S, MSQ and TooL are patient-reported outcomes, and guidance will be given to the patients on how to complete it/them.

9.7.1 4-Item Negative Symptom Assessment (NSA-4)

The NSA-4[21] 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.

9.7.2 Quality of Life Scale (QLS)

The QLS[23] is a clinician-rated scale designed to assess intrapsychic, social, and negative symptoms of schizophrenia and their consequences for 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 has a brief description of the judgement to be made and a set of suggested probes for the clinician. 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. 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.

9.7.3 Readiness for work questionnaire (WoRQ)

The WoRQ[24] 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 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.

9.7.4 Subjective Well-Being under Neuroleptic Treatment - short version (SWN-S)

The SWN-S[25] is a patient-rated scale designed to measure subjective effects of neuroleptic drugs to psychopathology, quality of life, and compliance over the past 7 days. The 20 items (10 positive and 10 negative statements) are grouped in 5 subscales (mental functioning,

self-control, physical functioning, emotional regulation and social integration), Each subscale contains 4 items, each item is rated on a 6-point Likert scale, from 1 (*not at all*) to 6 (*very much*). A score is calculated for each subscale, and the total score ranges from 20 to 120, where the higher score indicates better well-being.

It takes 5 to 10 minutes to complete the SWN-S.

9.7.5 Medication Satisfaction Questionnaire (MSQ)

The MSQ[26] 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.

9.7.6 Tolerability and Quality of Life questionnaire (TooL)

The TooL[27] 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.

9.7.6.1 Rater Qualification and Certification

The NSA-4, QLS, and WoRQ should be rated by a clinician, as defined above (see 9.1.3.2). Any exception must be discussed and approved by Lundbeck.

A NSA-4, QLS, and WoRQ training session will be organised prior to the start of the study.

Documentation of rater training and certification will be delivered to raters for archiving in the I-TMF. No patient should be rated before the documentation has been delivered.

New raters joining the study will be trained and certified using the same certification processes.

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

9.8 Biomarker Assessments

9.8.1 CYP2D6 and CYP2C19 Genotyping

Blood samples for CYP genotyping analysis will be collected in a EDTA tube (2x2mL). The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual*.

Based on *in vitro* examination of elimination routes for Lu AF35700, the following genetic variations for cytochrome P450 drug metabolising enzymes will be determined:

- CYP2C19: *1 (WT), *2, *3, *4, *5, *6, *7, *8, *9, *10 and *17
  Genotype result consists of 2 alleles from the list identified above.
- CYP2D6: *1 (WT), *2, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29 and *41
  Genotype result consists of 2 alleles from the list identified above. Duplication of an allele is reported by adding "XN" to the genotype result, however the assay does not allow for the determination of which allele is duplicated.

If relevant, the genotyping laboratory must report single nucleotide polymorphism (SNP) results, conclusive genotype, and inferred phenotype for each sample.

The blood samples will be analysed at a central laboratory using a validated method. The samples will be destroyed after they have been analysed.

The genotyping results will be used for exploratory interpretation of the efficacy and pharmacokinetic results; the genotyping results are not required at the time of inclusion in the study.

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

9.9 Exploratory Biomarker Assessments

9.9.1 General Considerations

Although the possible future exploratory biomarker analyses will help to increase our understanding of the aetiology of schizophrenia and TRS 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 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[43] to ensure patient privacy protection.

The results of the pharmacogenetics, proteomics/metabolomics and gene expression profiling will not be transferred nor reported.

9.9.2 Blood Sampling for Gene Expression Profiling

Blood samples for gene expression profiling (RNA) will be collected in two PAXgene tubes (2,5mL) at each time point. The maximum volume of blood to be collected during the study for this purpose will be 15 mL. Samples for gene expression profiling will be shipped to a Central Laboratory, United States for sample storage.

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

9.9.3 Blood Sampling for Metabolomic/Proteomic Biomarkers

Blood samples for metabolomic/proteomic biomarkers will be collected in one 10mL K2 EDTA tube at each time point. The maximum volume of blood to be collected during the study for this purpose will be 30 mL. The samples for metabolomic/proteomic biomarkers will be shipped to a Central Laboratory, United States, for sample storage.

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

9.9.4 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 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 and will not be relayed back to you or your study doctor. Your sample will be stored at a Central Laboratory, United States, for a maximum of 15 years after the overall end-of-the study. At that point it will be destroyed.

9.10 Order of Assessments

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

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

All visits other than Screening Visit:
- SWN-S, TooL and MSQ
- PANSS, NSA-4, QLS, PSP, C-SSRS and WoRQ
- CGI-S
- AIMS, BARS, and mSAS
- HEA

9.11 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 130 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 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 8.7) by a Central Laboratory.

The 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 8.7) 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.

9.12 Treatment Compliance

The responsible study personnel will dispense IMP. 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.

During Period A, the patient's treatment adherence to risperidone or olanzapine will be assessed by analysing the blood levels of risperidone plus 9-OH-risperidone or olanzapine. Please refer to Panel 2 for timing of sample.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[44]

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.

It is Lundbeck policy to collect and record all adverse events, including pre-treatment adverse events, that is, those that start after the patient has signed the *Informed Consent Form* and prior to the first dose of IMP.

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). Planned support hospitalisation (in the opinion of the investigator) of outpatients, or prolongation of hospitalisation of inpatients after having signed *Informed Consent Form* are not to be reported as SAEs. Adverse events occurring during a planned support hospitalisation of outpatients or during a prolongation of hospitalisation of inpatients are not to be reported as SAEs unless the AE fulfils other seriousness criteria than the hospitalisation. Symptoms which are expected as part of underlying disease should not be reported as AEs unless the symptoms increase in intensity or frequency.

In addition, in the following situations, the investigator has to consider reporting the outcome of the C-SSRS™ at any visit (starting with the Visit 2) as an SAE, if:

- the C-SSRS™ report indicates a suicidal ideation score of 4 or 5, respectively, or
- the patient answers "Yes" on any of the 5 C-SSRS™ suicidal behaviour items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behaviour).

Moreover, if the patient, in the opinion of the investigator, is at significant risk of suicide, whether fulfilling the C-SSRS™ criteria or not, this should also be reported as an SAE.

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*[4] or the UK *Summary of Product Characteristics* for risperidone[9] and olanzapine,[10] and related to an investigational product 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*.

For pre-treatment adverse events, a causality assessment is not relevant.

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*

10.2 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. If the patient becomes pregnant, the patient must be withdrawn from the study.

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:

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

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*[45] 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 a minimum, in the 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 GPV 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 inclusion 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 will 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.
- Risperidone (including 9-OH-risperidone) and olanzapine PK results will be transferred by central laboratory.
- The ECG results will be transferred by central ECG service provider
- If any electronic assessment tools (ie MINI, PANSS, CGI-S, PSP, mSAS, AIMS, BARS, NSA-4, QLS, WoRQ, C-SSRS) and/or patient reported outcomes (SWN-S, 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.

If 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 Inde*x, a certified copy of the *Patient Identification Code List*, a blank *Financial Disclosure Form* and a *Retrieval Form*.

If on-site storage is used, it must be included in the site's clinical trial agreement and the storage facility must meet Lundbeck requirements for onsite archival of the investigator TMF.

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 eCOA

Only patients with schizophrenia that are resistant to treatment (TRS) can be enrolled in this study. The main criterion to define TRS is a failure to respond to two antipsychotic treatment trials of adequate dose and duration. For the purpose of this study the first treatment failure will be documented retrospectively when a patient fails to respond to at least one antipsychotic treatment trial of at least 6 weeks duration, anytime in the past 2 years prior to Screening as described in Inclusion Criterion 8 (retrospective documentation). Furthermore, the failure to respond to the current antipsychotic treatment trial may be considered a retrospective failed treatment in compliance with Inclusion Criterion 8, if documented to be of adequate dose and duration.[46] Documentation of the second failed antipsychotic treatment trial will take place during the 6 weeks of Period A of the study (prospective confirmation).

The patient's medical records is the most comprehensive source to document antipsychotic treatment failure. Thus, it is required that the investigator attempts to obtain copies of previous medical records of psychiatric and general medical history for every patient. In case the investigator does not have medical records for a patient at his/her own clinic, the investigator should attempt to obtain copies/written summary of relevant medical records from the previous treating physician. If original medical records are unavailable, any properly documented communication with the treating physician, letters, written summaries, photocopies of medical records, pharmacy records and specific letter templates may be used to document at least one previous treatment failure, including the current antipsychotic treatment trial.

If the previous treating physician is no longer practicing and/or medical documentation has been destroyed as per local laws on archiving or by natural disaster, information from family members, caregivers or other persons close to the patient may help substantiating previous psychiatric history. Pharmacy records can be used to support the documentation of the dose and duration of treatment with a prescribed medication.

The investigator is advised to contact the study clinical surveillance team to discuss the cases with unavailable documentation.

If there is no acceptable reason for not obtaining documentation of previous medical history and/or attempts are not documented in the source documents, the patient should be considered not eligible for the study. In cases where sites do not document their effort to obtain the medical history, do not document summaries from previous treating physician or other sources, or do not document the reason the records are not available and there is no clear evidence that the patient is eligible, this will be considered an important protocol deviation.

To help in the assessment of eligibility and for documentation purposes, sites should prepare a Psychiatric History of the patient, including the information on failed antipsychotic treatment trials in the last two years gathered from all available sources. This brief Psychiatric History should be included in the Psychiatric Intake Note prepared for the Eligibility Review performed by the study clinical surveillance team.

The *Informed Consent Form* includes a statement whereby the patient agrees to the investigator communicating 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.

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 and/or randomisation 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

Symptoms of schizophrenia (primary endpoint for primary objective)

- Change from Baseline 2 (Period B) to study Week 16 in PANSS total score

16.2 Secondary Endpoints

Global clinical impression (supportive of primary objective)

- Change from Baseline 2 (Period B) to study Week 16 in CGI-S score

Functioning (secondary objective)

- Change from Baseline 2 (Period B) to study Week 16 in PSP total score

Response at Week 16 (supportive of primary objective)

Response criteria are blinded to investigators and described in *Clinical Study Protocol Addendum - Unmasked Information)*

16.3 Exploratory Endpoint(s)

Subjective well-being/quality of life and treatment satisfaction

- Change from Baseline 2 (Period B) to study Week 16 in SWN-S total score
- Change from Baseline 2 (Period B) to study Week 16 in MSQ score
- Change from Baseline 2 (Period B) to study Week 16 in TooL score
- Change from Baseline 2 (Period B) to study Week 16 in QLS score
- Change from Baseline 2 (Period B) to study Week 16 in WoRQ score

Symptoms of schizophrenia

- Change from Baseline 2 (Period B) to study Week 16 in NSA-4 total score

16.4 Safety Endpoint(s)

Safety and tolerability

- Adverse events
- Absolute values and changes from Baseline 2 in clinical safety laboratory tests, vital signs, weight, and ECG parameters
- Potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values
- C-SSRS categorisation
- Changes from Baseline 2 in mSAS, AIMS, and BARS total scores

17 Statistical Methodology

17.1 Responsibilities

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

The popPK analysis will be performed and reported separately by the Department of Quantitative Pharmacology, H. Lundbeck A/S.

17.2 Analysis Sets

The following analysis sets will be used to analyse and present the data:

- all-patients-treated set Period A (APTS_A) – all patients who took at least one dose of study medication during Period A (risperidone or olanzapine)
- all-patients-treated set (APTS) – all randomised patients who took at least one dose of double-blind study medication (Lu AF35700, risperidone, or olanzapine) after randomisation (Period B)
- full-analysis set (FAS) – all patients in the APTS who had a valid Baseline 2 assessment and at least one valid post-baseline 2 assessment of PANSS total score

The patients and data will be classified according to these definitions at a Classification Meeting held after all the data have been entered in the study database and verified and before the blind has been broken.

17.3 Descriptive Statistics

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

When the descriptive statistics are summarised by treatment group, summaries of the total population will also be reported.

17.4 Patient Disposition

Patient disposition will be summarised by treatment group and include the number of patients who completed the treatment period and the study and the number of patients who withdrew from treatment, as well as the number of patients in each analysis set (APTS_A, APTS, and FAS).

Disposition will be summarised for the APTS_A by risperidone/olanzapine therapy group and for the APTS by randomised treatment group.

The number of patients who withdrew from treatment will be summarised by treatment group and primary reason for withdrawal as well as by treatment group and all reasons for withdrawal.

Withdrawals during Period A will be summarised for the APTS_A by risperidone/olanzapine therapy group. Withdrawals during Period B will be summarised for the APTS by randomised treatment group.

17.5 Demographics and Other Baseline Characteristics

Demographics (sex, age, race), other baseline characteristics (height, weight, BMI, and mean waist circumference), and baseline efficacy variables will be summarised by treatment group.

Demographics will be summarised for the APTS_A by risperidone/olanzapine therapy group and for the APTS by randomised treatment group.

17.6 Recent and Concomitant Medication

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

Recent and concomitant medications will be summarised for the APTS_A by risperidone/olanzapine therapy group and for the APTS by randomised treatment group.

17.7 Exposure and Compliance

Exposure will be calculated per patient and summarised for the APTS_A by risperidone/olanzapine treatment group and for the APTS by randomised treatment group.

Compliance is defined as the percentage of planned medication taken by patients while enrolled in the study.

Compliance will be summarised for the APTS_A by risperidone/olanzapine therapy group and for the APTS by randomised treatment group.

Compliance during Period A will be summarised by risperidone/olanzapine therapy group for the responders, non-responders, and total patients in the APTS_A.

Descriptive statistics will be summarised for the final dose level of risperidone/olanzapine that patients were titrated to in Period A by risperidone/olanzapine therapy group for the ATPS.

17.8 Period A Evaluation

The percentage of patients responding to therapy at Weeks 1, 2, 4, and 6 as well as at any of those weeks will be summarised by therapy (risperidone/olanzapine) for APTS_A.

Response criteria are blinded to investigators and described in *Clinical Study Protocol Addendum - Unmasked Information).*

The efficacy variables collected during Period A will be summarised by week number for the total patients in APTS_A and by therapy (risperidone/olanzapine) for APTS_A.

17.9 Efficacy Analyses

17.9.1 General Efficacy Analysis Methodology

The efficacy analyses will be based on the FAS. A significance level of 0.05 is used unless otherwise indicated. For all endpoints, the effects of the two doses of Lu AF35700 will be evaluated by testing the null hypothesis of no difference to the active control for each dose.

17.9.2 Analysis of the Primary Endpoint

Changes from Baseline 2 (Week 6) in total PANSS score at Weeks 7, 8, 10, 12, 14, and 16, will be analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. All patients in the FAS will be included with their observed data in Period B. Data retrieved at Week 16 from withdrawals will not be included in the primary analysis.

The model will include the fixed, categorical effects of treatment (two doses of Lu AF35700 and active control), country, visit, treatment-by-visit interaction, Period-A-therapy (risperidone/olanzapine), Period-A-therapy-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order: first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The primary comparisons will be the contrasts between each dose and control at the Week 16 Visit based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between each dose and control based on this model will be reported with two-sided symmetric 95% confidence intervals and corresponding p-values.

17.9.3 Sensitivity Analyses of the Primary Endpoint

Some level of data missingness is expected, and the primary analysis (MMRM) is valid under the assumption that the data is Missing at Random (MAR). Simulation studies do suggest that MMRM is robust to accommodate some level of data Missing Not at Random. Since it is unclear how the level of missingness of this type of data will influce the outcome at this stage, choosing a pre-specified primary analysis valid under MNAR accurately will be very difficult.

As such, sensitivity analyses valid under relevant cases of data MNAR will be performed. In particular, pattern-mixture models will be used. Different delta (imputation of how much worse response patients who withdraw would have compared to those who complete the treatment period and who have the same profile up to time to withdrawal) will be applied as described by C. H. Mallinckrodt, Q. Lin, and G. Molenberghs.[47]

MMRM model as the primary analysis, including the retrieved data for withdrawals, will be performed.

The sensitivity analyses described above will be further specified in more detail in the statistical analysis plan (SAP).

17.9.4 Testing Strategy for Primary Endpoint

Hochberg's procedure will be used to control for multiplicity.

17.9.5 Analysis of the Secondary Endpoints

For CGI-S and PSP, the same methodology as that described for the primary endpoint will be used.

The proportion of patients responding at Week 16 will be compared for each dose versus control using logistic regression with Period A therapy, country and treatment as factors. The analysis will be done for observed cases without imputation as well as for the whole FAS, imputing non-response for all patients withdrawn prior to Week 16.

Additional responder analyses using alternative cut-points of the primary endpoint may be used to present the efficacy as measured by changes from Baseline 2 in PANSS total score.

17.9.6 Analysis of the Exploratory Endpoints

For NSA-4, SWN-S, MSQ, TooL, QLS scores and WoRQ the same methodology as that described for the primary endpoint will be used to analyse changes from Baseline 2 of total scores at Weeks 10 and 16.

17.9.7 Analysis of Subgroups

The analysis of the primary endpoint will be repeated by excluding patients with extremely low drug plasma concentrations (Lu AF35700/olanzapine/risperidone/ 9-hydroxy-risperidone) in Period B (Weeks 8, 10, and 16). Two analyses will be performed:

1. Include patients with values >LLOQ at Weeks 8, 10, and 16
2. Selection of patients based on population pharmacokinetic analysis. This analysis will be reported separately

17.9.8 Pharmacokinetic Analysis

Plasma concentrations of Lu AF35700 and its metabolite and CYP genotype will be summarised using descriptive statistics.

A *Population Pharmacokinetic Analysis Plan* describing the PK data handling and the planned popPK analysis will be prepared by the Department of Quantitative Pharmacology, H. Lundbeck A/S before the study is unblinded.

If deemed appropriate, the relationship between exposure and the primary efficacy endpoint might be investigated using a population pharmacokinetic/pharmacodynamic approach.

17.10 Safety Analyses

17.10.1 Analysis of Adverse Events

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

- *pre-treatment adverse event* – an adverse event that starts on or after the date the patient signed the *Informed Consent Form* and prior to the date of first dose of IMP
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts or increases in intensity on or after the date of first dose of IMP

Adverse events, sorted by system organ class (SOC) and preferred term, will be summarised by randomised treatment group for the APTS.

Allocation of TEAEs to Treatment Periods

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

17.10.2 Analysis of Other Safety Endpoints

Clinical safety laboratory tests, vital signs, weight/BMI, ECG parameters, and C-SSRS scores will be summarised by randomised treatment group using descriptive statistics. Potentially clinically significant (PCS) values will be flagged and summarised.

The changes from Baseline 2 in mSAS, AIMS, and BARS scores at Weeks 10 and 16 will be analysed using an MMRM model as described for the primary endpoint.

The CYP genotype will be listed.

All safety analyses will be based on the APTS.

17.11 Pharmacoeconomic Analyses

All pharmacoeconomic variables collected in the HEA will be summarised using descriptive statistics by treatment group and visit.

A separate analysis plan will be prepared for the pharmacoeconomic analyses.

17.12 Interim Analyses

No interim analyses are planned.

17.13 Sample Size and Power

A total of n=180 patients per group is needed in Period B to have 90% power for at least one Lu AF35700 dose to show a significant improvement on change in PANSS total score over the active control, assuming :

- a standard deviation (SD) of 20
- a mean improvement in PANSS total score of 5.25 and 7 for the 2 doses (standardised effect size 0.26 and 0.35) and
- use of Hochberg's procedure for multiplicity adjustment at 5% level of significance.

Assuming further an information loss of ~20% due to dropout in Period B, n=225 (=180/0.8) must be randomised, a total of 675 patients.

With an attrition rate of ~30% in Period A, approximately 964 (=675/0.7) patients are expected to be enrolled to meet the target of randomising 675 patients in Period B.

A blinded re-assessment of sample size will be considered if the blinded SD estimate or the dropout rate deviates from the assumptions. This re-assessment will be performed when 50% of the patients have completed the treatment period. A maximum of 300 randomised patients per treatment arm will be allowed in the study. The pooled standard deviation will be estimated from the Covariance Parameter Estimates from an MMRM model identical to the one to be used for the primary analysis, except without the effect of treatment, i.e. the following:

The model will include the fixed, categorical effects of country, visit, Period-A-therapy (risperidone/olanzapine), Period-A-therapy-by-visit interaction as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors.

17.14 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, before the study is unblinded.

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).[48]

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.

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Appendix I

Clinical Study Protocol Authentication and Authorisation

Clinical Study Protocol
Authentication and Authorisation

Study title:	Interventional, randomised, double-blind, active-controlled, fixed-dose study of Lu AF35700 in patients with Treatment-resistant Schizophrenia
Study No.:	16159A
Edition No.:	4.0
Date of edition:	27 June 2017

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 of Biostatistics:	[redacted]
Head of Risk Management, Pharmacovigilance:	[redacted]

Authorisation

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

Head of CRD 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
Any investigational drug	– Prohibited <30 days before Baseline 1
Antidepressants	– Prohibited <7 days before Baseline 1 (fluoxetine: <28 days)
Anticonvulsants	– Prohibited <7 days before Baseline 1
Antipsychotics	– Prohibited after the end of the down-tapering of current antipsychotic medication, (end of Week 1). – Patients currently receiving depot or long-acting antipsychotics can be enrolled after an adequate discontinuation period, defined as skipping one full treatment cycle plus 3 days (See "Study Methodology, Period A")
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: benztropine (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.
Anxiolytics and hypnotics	If the patient receives anxiolytic or hypnotic therapy prior the Screening Visit, 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 or emergent agitation, dose adjustment of currently prescribed anxiolytic medication is recommended if applicable. If new medication is initiated, short-acting benzodiazepines such as lorazepam (up to 8 mg/day, orally or intramuscularly), oxazepam (up to 80 mg/day, orally), and alprazolam (up to 4 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.
Non-benzodiazepine sleep aids	– Non-benzodiazepine sleep aids are allowed, provided doses are stable ≥6 weeks prior to Baseline 1.
Mood stabilizers	– Prohibited <7 days before Baseline 1. Except valproic acid which should be tapered down carefully and be completed ≥2 days prior to Baseline 1.
Varenicline	– Prohibited <7 days before Baseline 1
Barbiturates	– Prohibited

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 with the exception of the prophylactic use of aspirin; NSAIDs may be used episodically
Psychotropic agents not otherwise specified	– Prohibited – Cough preparations containing ephedrine, pseudoephedrine and codeine are allowed for treatment duration for a maximum of 1 week
Dopamine depleting agents	– Prohibited <7 days before Baseline 1
Antihistamines	– Antihistamines except loratadine, desloratidine, cetirizine, levocetirizine, mizolastine and fexofenadine are prohibited
Steroids	– Systemic use is prohibited, inhaled and topical use is allowed
Hormones	– Prohibited except for thyroid hormone replacement, contraceptives (e.g. implants, injectables, combined oral contraceptives), estrogen and progesterone replacement therapy as well as benign prostatic hyperplasia treatment.
Vitamins, nutritional supplements, and non-prescritpion herbal preparations	– Prohibited during the study, unless approved in advance by the Medical Monitor
Potent CYP2D6 inhibitors	– See Panel for Prohibited CYP sub-enzyme influencing medications below
Potent CYP1A2 inhibitors	– See Panel for Prohibited CYP sub-enzyme influencing medications below
Potent CYP3A4 inducers	– See Panel for Prohibited CYP sub-enzyme influencing medications below
Hydroxyzine and diphenhydramine (not allowed for the treatment of agitation, anxiety, insomnia or EPS)	– Except for short term treatment (<14 days) of allergy
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

Prohibited CYP sub-enzyme influencing medications

Selected CYP2D6 Inhibitors	
Celecoxib Chloroquine Chlorpheniramine Clemastine Diphenhydramine[a] Fluoxetine Halofantrine	Hydroxyzine[a] Methadone Paroxetine Pyrilamine Quinidine Terbinafine Tripelennamine
Selected CYP1A2 Inhibitors	
Ciprofloxacin Enoxacin Fluvoxamine	
Selected CYP3A4 Inducers	
Armodafinil Bosentan Carbamazepine Efavirenz Etravirine	Modafinil Nafcilin Phenytoin Rifampicin

[a] Short term use for allergy is permitted as described in table for Disallowed and restricted medications during the study