Clinical Study Protocol

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

Lu AF35700

Study No.:	17303A (Anew)
EudraCT/IND:	2017-000788-34 (EU)/ 116,335 (US)
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
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Synopsis – Study 17303A

Sponsor	**Investigational Medicinal Product**	**EudraCT/IND No.**
H. Lundbeck A/S	Lu AF35700	2017-000788-34 / 116335

Title of Study

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

Study Sites and Number of Patients Planned

Approximately 100 sites in US, Europe, Japan, or South America are planned (in-/outpatient clinics).

Approximately 490 patients in US, Europe, Japan, or South America are planned for randomization with 245 randomized patients per treatment group.

Objectives

- Primary objective:
  - to assess the efficacy of Lu AF35700 on symptoms of schizophrenia in patients with early-in-disease (ED) or late-in-disease (LD) treatment-resistant schizophrenia (TRS)
- Secondary objectives:
  - to assess the efficacy of Lu AF35700 on symptoms of schizophrenia in patients with ED TRS
  - to assess the efficacy of Lu AF35700 on negative symptoms of schizophrenia in patients with ED or LD TRS
- Exploratory objectives:
  - to assess the efficacy of Lu AF35700 in patients with ED TRS *versus* patients with LD TRS
  - to assess the efficacy of Lu AF35700 in patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit *versus* patients with LD TRS
  - to assess the efficacy of Lu AF35700 in patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
  - to assess the effect of Lu AF35700 on cognitive performance and functioning in patients with ED TRS, LD TRS, or patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
  - to explore patient historical and demographic characteristics predictive of response to treatment with Lu AF35700
  - to explore genetic markers (genotype and expression) predictive of, or associated with, response to treatment with Lu AF35700
- Safety objective:
  - to evaluate the safety and tolerability of Lu AF35700 in patients with ED or LD TRS

Study Methodology

- This is an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, active-controlled, fixed-dose study.
- The study is planned to include patients from US, Europe, Japan, or South America.
- In total, 490 patients will be randomized.
- In this study patients are blinded to any transition in care from Period A to Period B; specifically, the patients are kept blinded to the time point of randomization at Baseline 2 and to the treatment that they may receive during this study. In addition, patients must remain blinded to any association with their response to the treatment and their continuation in the study.
- The study will consist of 4 Periods:

1. Screening Period

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

2. Period A – Prospective Confirmation Period (6 weeks)

Patients, who meet the pre-specified selection criteria for either ED or LD TRS, will enter a single (patient)-blinded treatment period with risperidone or olanzapine to confirm their resistance to antipsychotic drug treatment.

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-hydroxy-risperidone; Invega™) in the most recent treatment trial, or in a documented treatment failure in the past 2 years, or have a documented history of intolerance to risperidone (or 9-hydroxy-risperidone; Invega™) treatment in the past 2 years, 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. For patients treated with risperidone or Invega™ more than 2 years ago and for whom the treatment resulted in an inadequate response or intolerance to the treatment, the investigator may consult with Lundbeck and/or its designee whether such patients may receive olanzapine; this decision must be approved by Lundbeck and/or designee. Current antipsychotic drug treatment will be down-tapered within the first 7 days of Period A. Thereafter the dose of olanzapine may be adjusted up once from 15 to 20 mg/day during Weeks 3 and 4, according to the investigator's clinical judgement. If necessary for tolerability, dose may be decreased once back to 4 mg/day risperidone, or 15 mg/day olanzapine, during Weeks 3 and 4. No dose adjustments are allowed during the last 2 weeks (5 and 6) of Period A. Patients currently treated with 'depot' antipsychotics 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 (inclusion criteria blinded to site and patient) will be withdrawn from the study.

3. Period B – Double-blind Treatment Period (8 weeks)

Patients who fulfil the entry criteria Period B will enter the double-blind treatment period (Period B) at Baseline 2. The specific inclusion criteria for Period B will be blinded to the site and patient. Patients will be randomly assigned (1:1) to 8 weeks of double-blind treatment with either Lu AF35700 (10 mg/day) or to continue their treatment with risperidone or olanzapine at a dose set at the end of Week 4 (Visit 5) of Period A. The randomization will be stratified by duration of disease (ED and LD). Patients with ED or LD TRS will be enrolled such that an approximate 1:2 ratio is achieved.

Patients who complete the study treatment until Visit 11 (Primary Outcome) may be eligible to enter a 52-week, open-label extension study.

Study Methodology (continued)

The dose of Lu AF35700, risperidone or olanzapine will be fixed throughout Period B (Lu AF35700: 10 mg/day; risperidone: 4 mg/day or 6 mg/day, determined in Period A; olanzapine: 15 mg/day or 20 mg/day, as determined in Period A). For patients randomized to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion during the initial 7 days of Period B.

4. Safety Follow-up Period (6 weeks)

All patients, including those who prematurely discontinue will be scheduled for a Safety Follow-up Visit for safety assessments 6 weeks after the last dose of IMP, with the exception of those patients entering the optional open-label extension study.

Efficacy Follow-up (14 weeks)

Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will, in addition to the Withdrawal Visit, also be asked to attend an Efficacy Follow-up Visit (Visit 13), for assessment of efficacy, safety and concomitant medication. This visit coincides with the time point of the Primary Outcome Visit (Week 14) that should have taken place, had the patient not been withdrawn from the study.

The study design is presented in Panel 1 and the scheduled assessments are summarized in Panel 2.

Target Patient Population

The target population for randomization in the current study is patients with treatment-resistant schizophrenia. Patients to be enrolled in the current study should fulfil either the criteria for ED TRS or LD TRS. The study population will be patients from US, Europe, Japan, or South America.

Key Inclusion Criteria – Period A

Criteria for Patients with ED TRS

- The patient has schizophrenia, first diagnosed <10 years prior to the Screening Visit and according to DSM-5™ and confirmed by the Mini International Neuropsychiatric Interview (MINI)

Criteria for Patients with LD TRS

- The patient has schizophrenia, first diagnosed ≥10 years prior to the Screening Visit and according to DSM-5™ and confirmed by the Mini International Neuropsychiatric Interview (MINI)

General Criteria (Both Patients with ED and LD TRS)

- The patient is a man or woman, aged ≥18 years.
- The patient is receiving treatment with a psychiatrist in either an inpatient or outpatient facility.
- The patient has been treated with adequate dose(s) of antipsychotic drug treatment for at least 2 weeks prior to the Screening Visit.
- The patient has failed to show an adequate response in the level of psychotic symptoms during at least one documented treatment trial with an adequate dose of an antipsychotic drug prescribed for an adequate time (at least lasting for 6 weeks) within 2 years prior to the Screening Visit. The failure to respond to the current antipsychotic drug treatment trial may be considered a retrospective failed treatment, if the patient has been treated for 6 weeks with adequate dose(s) of antipsychotic drug(s).
- The patient has a PANSS total score of ≥80 (on 1-7 scale) and a score of ≥4 (≥ "Moderate" on 1-7 scale) on at least 2 of the following PANSS items at the Screening and at Baseline 1 [Week 0] Visits.
  - P2 – Conceptual disorganization
  - P3 – Hallucinatory behaviour
  - P6 – Suspiciousness/persecution
  - G9 – Unusual thought content; AND
- The patient has a CGI-S score of ≥4 (≥"Moderately ill") at the Screening and at Baseline 1 (Week 0) Visits.

Target Patient Population (continued)

Entry Criteria – Period B

- The patient has completed Period A of the study
- Response criteria, blinded to site and patient and described in the *Clinical Study Protocol Addendum – Unmasked Information,* are satisfied.
- Patient is considered to have been adherent with assigned medication in Period A. Adherence is assumed based upon taking at least 80% of assigned IMP during Period A.
- The patient's designation as ED TRS or LD TRS does not invalidate the *a priori* specified stratification plan for patients randomized into Period B

Investigational Medicinal Products, Doses and Mode of Administration

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

Risperidone – 2, 4, and 6 mg/day, encapsulated tablets, orally, once daily

Olanzapine – 5, 10, 15, and 20 mg/day, encapsulated tablets, orally, once daily

Placebo – encapsulated tablets, orally, once daily

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: The two capsules will be taken together in the morning or evening based on the patients' preference. The first dose is to be taken the day after IMP has been dispensed to the patient.

Period A – Prospective Treatment Period

- Patients will be initiated on the lowest dose and titrated up to 6 mg/day risperidone, or if recently failed on risperidone, up to 15 mg/day olanzapine during the first week according to the following scheme:
  - Risperidone: 2 mg/day for the first 2 days; then 4 mg/day for the next 2 days ; 6 mg/day for the last 3 days. If necessary for tolerability, the dose may be decreased once back to 4 mg/day during Weeks 3 and 4. The dose must not be adjusted during Weeks 5 and 6.
  - Olanzapine: 5 mg/day for the first 2 days; then, 10 mg/day for the next 2 days; then, 15 mg/day for the last 3 days. The dose may be increased once to 20 mg/day at during Weeks 3 and 4. If necessary for tolerability, the dose may be decreased once back to 15 mg/day during Weeks 3 and 4. The dose must not be adjusted during Weeks 5 and 6.
- The last possible time point for dose adjustment is at Visit 5.

Period B – Double-blind Treatment Period

- Patients randomized to Lu AF35700 will be initiated with 10 mg/day Lu AF35700 without titration during the first week.
- Patients randomized to continued treatment (risperidone or olanzapine) will be treated with the same dose during Period B as set at the end of Week 4 (Visit 5) of Period A.
- For patients randomized to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion and completed in the 7 days following the baseline for Period B (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

Investigational Medicinal Products, Doses and Mode of Administration (continued)

Discontinuation of IMP

- Discontinuation of IMP will be initiated at the Primary Outcome or Withdrawal Visit for all patients who discontinue the study for any reason after Week 1 of Period A or anytime during Period B. The investigator has the option to discontinue IMP through down-titration (recommended) or to stop IMP abruptly for safety or tolerability issues. Down-titration proceed according to the following scheme:
  - Risperidone (4 mg/day): 2 mg/day for the first 4 days; placebo for the 3 subsequent days
  - Risperidone (6 mg/day): 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

Discontinuation of IMP during the first week of Period A will be abrupt

Efficacy Assessments

- Positive and Negative Syndrome Scale (PANSS) – Total Score, and:
  - PANSS – Positive Factor Score (Marder Positive Score)
  - PANSS – Negative Factor Score (Marder Negative Score)
- Clinical Global Impression – Severity of Illness (CGI-S)
- 16-item Negative Symptom Assessment (NSA-16)
- Personal and Social Performance Scale (PSP)
- Brief Assessment of Cognition in Schizophrenia (BACS)
- Demographic and Historical Predictors of Response, including:
  - Number of years from first schizophrenia diagnosis
  - Premorbid Adjustment Scale (PAS)
  - Number of failed antipsychotic drug (APD) treatment episodes

Pharmacoeconomic Assessments

- Subjective Well-being Under Neuroleptic – short version (SWN-S)
- Drug Attitude inventory-10 (DAI-10)

Pharmacokinetic Assessments

Blood samples will be collected during the study for:

- Pharmacokinetic analyses of Lu AF35700 and its major metabolite (Lu AF36152)
- Analyses of plasma levels of olanzapine and risperidone plus 9-hydroxy-risperidone
- CYP genotyping

Safety Assessments

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

Biobanking

- Mandatory blood samples are collected for possible future for gene expression profiling and metabolomic/ proteomic exploratory biomarkers analysis at time points specified in Panel 2.
- Optional blood samples are collected for in-study and possible future DNA extraction and pharmacogenetics analysis at time point specified in Panel 2.
- Optional blood samples are collected for separation of peripheral blood mononuclear cell (PBMC) to facilitate possible future generation of induced Pluripotent Stem Cells lines. Patients consenting for PBMC separation must undergo mandatory infectious disease testing (IDT), that is blood samples must be collected and tested for HIV, HBV, and HCV.

Endpoints

- Primary endpoint:
  - symptoms of schizophrenia (primary endpoint for primary, secondary, and exploratory objectives)
    - change from Baseline 2 to Week 14 in PANSS total score
- Key secondary endpoints
  - global clinical impression (supportive of primary and secondary objectives)
    - change from Baseline 2 to Week 14 in CGI-S score
  - functioning (supportive of explorative objective)
    - change from Baseline 2 to Week 14 in PSP total score)
- Secondary endpoints:
  - proportion of responders at Week 14 (supportive of primary and secondary objective).
    - Responders criteria will be blinded to investigator and described in the *Clinical Study Protocol Addendum- Unmasked Information*.
  - negative symptoms (supportive of secondary objective)
    - change from Baseline 2 to Week 14 in NSA-16 total score
    - change from Baseline 2 to Week 14 in PANSS Negative Factor Score (Marder Negative Score)
- Exploratory endpoints:
  - cognitive performance (supportive of explorative objective)
    - change from Baseline 2 to Week 14 in BACS score
  - analysis of patient historical and demographic predictors of response (supportive of exploratory objective), in:
    - Patients with ED TRS
    - Patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
    - Patients with ED TRS *versus* LD TRS
    - Patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit *versus* patients with LD TRS
  - event-related potentials (mismatch negativity; supportive of exploratory objective) - assess correlations between effects on mismatch negativity and treatment response in:
    - Patients with ED TRS
    - Patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
    - Patients with ED TRS *versus* LD TRS
    - Patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit *versus* patients with LD TRS
- Genetic analysis (for example CYP genotyping and polygenetic risk-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

Statistical Methodology

- The following analysis sets will be used to analyse and present the data for each of the above groups of patients:
  - all-patients-treated set Period A (APTS_A) – all patients who took at least one dose of IMP during Period A (risperidone/olanzapine)
  - all-patients-treated set (APTS) – all randomized patients who took at least one dose of double-blind IMP (Lu AF35700 or risperidone/olanzapine) after randomization (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 two-sided significance level of 0.05 is used unless otherwise indicated. For all endpoints, the effects of Lu AF35700 will be evaluated by testing the null hypothesis of no difference to the active control.
- Testing strategy
  - If Lu AF35700 is superior to risperidone/olanzapine for the primary endpoint, the null hypothesis of no difference between Lu AF35700 compared to risperidone/olanzapine will be tested for the key secondary endpoints in the following order:
    - 1. Change from Baseline 2 to Week 14 in CGI-S score
    - 2. Change from Baseline 2 to Week 14 in PSP total score
  - Change in PSP will only be tested if Lu AF35700 is superior to risperidone/olanzapine for CGI-S.
- Analysis of the primary endpoint:
  - Changes from Baseline 2 (Week 6) in total PANSS score at Weeks 7, 8, 10, 12, and 14 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 14 from withdrawals will not be included in the primary analysis. The model will include the fixed, categorical effects of treatment (Lu AF35700 and risperidone/olanzapine), strata, country, visit, treatment-by-visit interaction, stratum-by-visit interaction, fixed covariates of baseline scores (Baseline 1 and Baseline 2) and baseline scores-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, the following within-patient (co)variance structures will be applied in the listed 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 difference between Lu AF35700 and risperidone/olanzapine at Week 14 based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between Lu AF35700 and risperidone/olanzapine based on this model will be reported with two-sided symmetric 95% confidence intervals and corresponding p-values.
  - Supportive of secondary and exploratory objectives;
  - The changes in PANSS total score from Baseline 2 (Week 6) to Week 14 for In patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit, ED TRS, LD TRS, ED TRS *versus* LD TRS, and patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit *versus* patients with LD TRS will be examined using the same methodology as that described for the primary endpoint. The model will include the fixed, categorical effects of treatment (Lu AF35700 and risperidone/olanzapine), subgroup, country, visit, treatment-by-visit-by-subgroup interaction, and fixed covariates of baseline scores (Baseline 1 and Baseline 2) and baseline scores-by-visit interaction. The patients will be classified into subgroups according to whether they were first diagnosed with schizophrenia ≤5 years prior to the Screening Visit, between 5 and 10 years prior to the Screening Visit, or ≥10 years prior to the Screening Visit. From this model, the difference between treatments within each subgroup at Week 14 will be derived from the treatment-by-visit-by-subgroup interaction. Also, this interaction will be used to explore the efficacy in ED TRS *versus* LD TRS by estimating of (Lu AF35700 ED – risperidone/ olanzapine ED) *versus* (Lu AF35700 LD – risperidone/olanzapine LD). In the same way,

Statistical Methodology (continued)

the efficacy in patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit versus LD TRS will be explored.

- Analysis of the secondary endpoints:
- For CGI-S, NSA-16, and PANSS Negative Factor Score, the same model as that described for the primary endpoint will be used.
- The proportion of patients responding at Week 14 will be compared for Lu AF35700 *versus* risperidone/olanzapine using logistic regression with strata, country and treatment as factors and baseline PANSS total scores (Baseline 1 and Baseline 2) as covariates. The analysis will be done for observed cases without imputation using the FAS, as well as imputing non-response for all patients discontinued prior to Week 14. The definition of response will be defined in the *Clinical Study Protocol Addendum – Unmasked Information.*

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

- Analysis of the exploratory endpoints:
  - For BACS and PSP, the same model as that described for the primary endpoint will be used.
  - The proportion of patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit, patients with ED TRS or LD TRS, the difference between patients with ED TRS and those with LD TRS, and the difference between patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit and those with LD TRS responding at Week 14 will be compared for Lu AF35700 *versus* risperidone/olanzapine using logistic regression with country as factor and treatment-by-subgroup interaction and baseline PANSS total score as covariate. The analysis will be done for observed cases without imputation using the FAS, imputing non-response for all patients discontinued prior to Week 14.
  - The effect of potential demographic and historical predictors of response (number of years from first schizophrenia diagnosis, and number of failed AP treatment episodes) will be investigated for the primary and secondary endpoints. MMRM and logistic regression models similar to those described above will be applied with the different predictors included as factors or covariates, both interacting with treatment, as appropriate. These analyses will be detailed in the statistical analysis plan.
  - The effect of genetic analysis will be investigated for the primary and secondary endpoints. These analyses will be detailed in a separate protocol and statistical analysis plan, and will be reported separately.
  - Plasma concentrations of Lu AF35700 and metabolite Lu AF36152, risperidone and 9-hydroxy-risperidone, olanzapine will be summarized using descriptive statistics and may be used in population pharmacokinetic analyses (to be reported separately).
- 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 discontinue would have compared to those who do complete the study and who have the same profile up to time to withdrawal) will be applied. These analyses will be detailed in the statistical analysis plan.
  - The primary analysis will be repeated for the subgroup of patients that were randomized after protocol amendment PA3 was approved in the relevant country.
- Analysis 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 summarized using descriptive statistics.

Patient disposition and demographics will be summarized using descriptive statistics.

Sample Size Considerations

The study will include 245 randomized patients per group in Period B.

Assuming a common standard deviation of 15, there is approximately 93% power for showing a mean improvement in change in PANSS total score of 5.25 (standardized effect size 0.35) of Lu AF35700 over risperidone/olanzapine with 196 patients per treatment arm.

Assuming an information loss of ~20% due to dropout in Period B, n=245 (=196/0.8) will be randomized to each treatment group, bringing the total number of randomized patients to 490.

With an attrition rate of ~40% in Period A, approximately 817 (=490/0.6) patients are expected to be enrolled to meet the target of randomizing 490 patients in Period B.

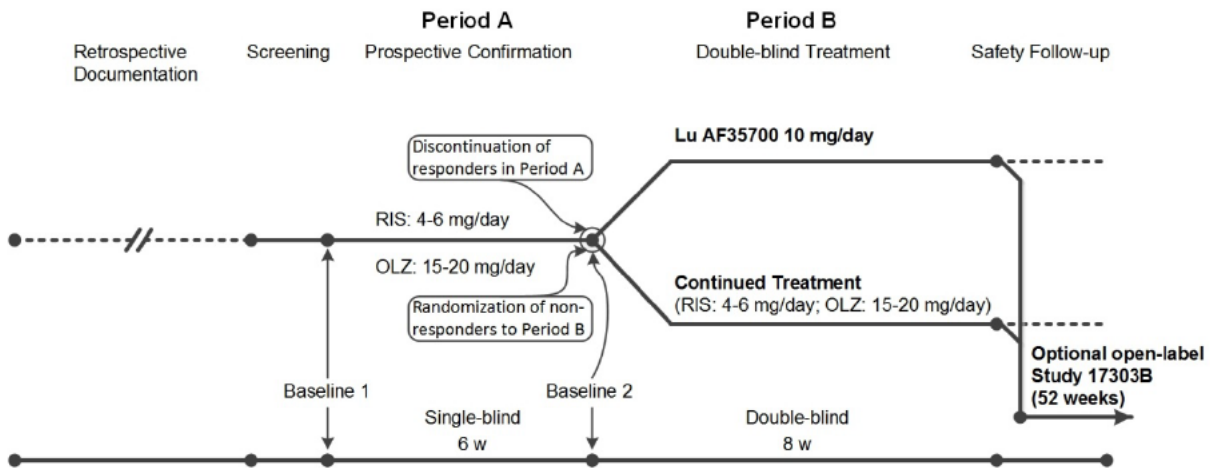
A blinded re-assessment of sample size will be considered if the blinded standard deviation estimate or the dropout rate deviates from the assumptions. A maximum of 300 randomized patients per treatment arm will be allowed in the study. The pooled standard deviation will be estimated from the Covariance 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, stratum-by-visit interaction as well as the fixed covariates of baseline scores (Baseline 1 and Baseline 2) and baseline scores-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors.

Ethical Rationale for Study and Study Design

- This study will be conducted in compliance with the principles of *Good Clinical Practice*.
- 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.
- Targeted enrolment and stratification of patients with ED TRS and LD TRS, as defined in this protocol, may increase the understanding of how Lu AF35700 may be an effective treatment across the longitudinal course of disease.
- Given the unique receptor binding profile of Lu AF35700 characterized by a high affinity to dopamine D_1 and serotonin 5-HT_6 receptors combined with a low level of dopamine D_2 interaction, Lu AF35700 has the potential to offer an effective alternative treatment option for patients with treatment resistant schizophrenia.
- Based on data from the ongoing clinical pharmacology programme in healthy subjects and patients with schizophrenia, the dose used in the current study is considered to be safe and well tolerated.
- The aim of the study is to generate supporting evidence for efficacy and safety of Lu AF35700 in patients with TRS. 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 recommendations provided for conducting studies in patients with TRS as outlined in the EMA guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia.
- In the current study, eligible patients who have had a recent treatment failure will enter a single (patient)-blinded confirmation period and initiate a treatment trial with risperidone or olanzapine (well-known and widely used antipsychotic drugs, to assess treatment response. Only patients where a lack of adequate treatment response is confirmed will be randomized to double-blind treatment with either Lu AF35700 or to continued treatment (risperidone or olanzapine) for a period of 8 weeks. Patients who respond to the initial treatment with risperidone or olanzapine will be excluded from the study. Thus, approximately half of the non-responding patients will be randomized back to the failed treatment used in the initial period of the current study. This study design is considered ethically justifiable given the limited treatment options for this patient population and the need to utilize a rigorous scientific design to develop new safe and effective treatments for TRS. Blinding of the patients and of the investigators, as described in the study design, to actual treatment received reduces bias that would otherwise be introduced and that may influence the reliability of the study results.
- The duration of the double-blind treatment period in the current study is 8 weeks in order to provide sufficient time to determine the extent of attainable symptom reduction and allow safety evaluation. In general, an adequate treatment trial in TRS should have a minimum duration of 6 weeks. The 8-week duration in this study further allows adequate time for patients to receive Lu AF35700 under steady state conditions while their response is being assessed. 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. Patients who complete the study treatment until Visit 11 (Primary Outcome) may be eligible to enter a 52-week, open-label extension 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. Patients enrolled in the current study will be scheduled for a Safety Follow-up Visit 6 weeks after last dose of IMP for those who do not enter the open-label extension study.
- 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



NOTE: Randomized patients will be stratified in Period B to ensure equal distribution of patients with ED TRS and LD TRS in the two treatment arms (targeted ratio between patients with ED TRS to LD TRS is 1:2).

Panel 2 Study Procedures and Assessments

Visit	Informed consent[a]	Screening[b]	Baseline 1[c]				Baseline 2[c]					Primary Outcome[d] or Withdrawal[e]	Safety Follow-up[f]	Efficacy Follow-up[g]
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12	13
End of Week			0	1	2	4	6	7	8	10	12	14	20	14
Day		-21/-1	0	7	14	28	42	49	56	70	84	98	140	98
Visit Window (days)[h]				±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±3
Signed informed consent	√													
Screening/Baseline Procedures and Assessments														
Diagnosis (DSM-5™)		√												
MINI		√												
Disease-specific history[i]		√												
Relevant social, medical and psychiatric history		√												
Demographics (age, sex, race)[j]		√												
Alcohol and substance use		√												
Height		√												
Family psychiatric history		√												
Prior antipsychotic and disallowed medication washout		√												
Inclusion/exclusion criteria		√	√											
Entry criteria Period B							√							
PAS							√							
Blood sampling for CYP2D6 and CYP2C19 genotyping							√							
Blood sampling for pharmacogenetics (optional)[k]							√							
Randomization							√							
Efficacy Assessments														
PANSS		√	√	√	√	√	√	√	√	√	√	√		√
CGI-S		√	√	√	√	√	√	√	√	√	√	√		√
NSA-16			√				√			√		√		
BACS[l]			√				√					√		
PSP			√				√			√		√		
Pharmacoeconomic Assessments														
SWN-S (PRO)							√					√		
DAI-10 (PRO)							√					√		

Visit	Informed consent[a]	Screening[b]	Baseline 1[c]				Baseline 2[c]					Primary Outcome[d] or Withdrawal[e]	Safety Follow-up[f]	Efficacy Follow-up[g]
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12	13
End of Week			0	1	2	4	6	7	8	10	12	14	20	14
Day		-21/-1	0	7	14	28	42	49	56	70	84	98	140	98
Visit Window (days)[h]				±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±3
Pharmacokinetic Assessments														
Blood sampling for Lu AF35700 and metabolite or olanzapine, risperidone and 9-hydroxy-risperidone quantification[m]					√	√	√		√	√		√		
Biobanking														
Blood sampling for gene expression profiling (RNA)[n]			√		√		√			√		√		
Blood sampling for metabolomics/proteomics (plasma)[n]			√		√		√			√		√		
Blood sampling for pharmacogenetics (optional)[o]			√											
Blood sampling for PBMC separation (optional)[p]			√											
Blood sampling for Infectious Status Testing (HIV, HBsAg, anti-HCV)[q] (only patients enrolled for PBMC collection)			√											
Safety Assessments														
Adverse events[r]		√	√	√	√	√	√	√	√	√	√	√	√[s]	√[s]
Blood and urine sampling for clinical safety laboratory tests (fasting)		√			√		√		√	√		√	√[t]	
Serum prolactin[u]			√				√					√		
HBA_{1c} (fasting)		√					√					√		
Blood lipid profile (fasting)		√					√					√		
Vital signs		√	√	√	√	√	√	√	√	√	√	√		
ECGs		√					√		√	√		√		
Body weight		√	√				√					√		
Waist circumference			√				√					√		
Physical Examination			√									√		
C-SSRS		√	√	√	√	√	√	√	√	√	√	√	√	

Visit	Informed consent[a]	Screening[b]	Baseline 1[c]				Baseline 2[c]					Primary Outcome[d] or Withdrawal[e]	Safety Follow-up[f]	Efficacy Follow-up[g]
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12	13
End of Week			0	1	2	4	6	7	8	10	12	14	20	14
Day		-21/-1	0	7	14	28	42	49	56	70	84	98	140	98
Visit Window (days)[h]				±3	±3	±3	±3	±3	±3	±3	±3	±3	+3	±3
Other Study Procedures														
IMP dispensed			√	√	√	√	√	√	√	√	√	√[v]		
Possible change in IMP[w]					√	√								
IMP returned and accountability				√	√	√	√	√	√	√	√	√	√	
Recent and concomitant medication		√	√	√	√	√	√	√	√	√	√	√	√	√
Days of Hospitalization		√	√	√	√	√	√	√	√	√	√	√	√	√
Urine drug screen[x]		√				√						√		
Pregnancy tests[y]		√										√		
Urine pregnancy tests[y]							√							
[Country-specific Protocol Amendment 1 for UK: Urine pregnancy tests[y]]			√			√	√			√				

C-SSRS = Columbia-Suicide Severity Rating Scale; MINI = Mini International Neuropsychiatric Interview; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event

a *Informed Consent Forms* must be signed before any study-related procedures are initiated, including washout of disallowed medications.

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 In this study patients are blinded to any transition in care from Period A to Period B; specifically, the patients are kept blinded to the time point of randomization at Baseline 2 and to the treatment that they may receive during this study. In addition, patients must remain blinded to any association with their response to the treatment and their continuation in the study.

d For patients consenting and entering directly into the open label extension study (Study 17303B), the Primary Outcome Visit of Study 17303A will coincide with the Baseline Visit of Study 17303B.

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

f This may be a telephone contact, unless an SAE has occurred since the previous visit or unless there was a clinically significant out-of-range safety laboratory test value at the previous visit, and will be done only for patients who do not enter the open-label extension study. 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).

g This visit is only for patients that withdraw from Period B of the study before the scheduled Primary Outcome Visit (Week 14). 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 14) for the assessment of efficacy, safety and concomitant medication. If patient attends the Withdrawal Visit 5 days prior to week 14 (planned Primary Outcome Visit) the patient should not be asked to come for an Efficacy Follow-up Visit.

h If the date of a patient visit does not conform to the study plan, subsequent visits must be planned to maintain the visit schedule relative to the Baseline 1 Visit.

i Includes Premorbid Adjustment Scale.

j The patient's demographics information (age, sex, race) is to be recorded in the eCRF at *Informed Consent Form* signature date.

k Informed Consent process for in-study pharmacogenetic testing is covered in section 4.2. For patients not qualifying for study period B this sample must be discarded.

l BACS is applicable for US and Europe only.

m The blood samples for Lu AF35700 and metabolite or olanzapine, risperidone and 9-hydroxy-risperidone analysis should be drawn in association to the blood sampling for clinical safety laboratory tests (as applicable). Lu AF35700 and the major metabolite Lu AF36152 will only be analysed in samples from Visits 8, 9, and 11. Olanzapine, risperidone and 9-hydroxy-risperidone will be analysed in all six samples.

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

o Sampling for pharmacogenetics is optional and a separate *Patient Information Sheet* and *Informed Consent Form* covers this analysis. See section 4.2. Sampling may be scheduled to another visit if needed.

p Sampling for PBMC collection (US only) for possible future generation of induced pluripotent stem cells lines is optional and a separate *Patient Information Sheet* and *Informed Consent Form* covers this. Sampling may be scheduled to another visit if needed.

q Sampling for Infectious Disease Testing refer only to patients enrolled for PBMC collection for which this is mandatory and will be addressed in the separate *Patient Information Sheet/Informed Consent Form* referring to the PBMC collection.

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

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

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

u Results will remain blinded throughout the study.

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

w The dose of IMP can be increased for efficacy or decreased for tolerability at scheduled or unscheduled visits during weeks 3 and 4. Last possible time point for dose adjustment is at Visit 5.

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

y S-βhCG pregnancy test should be performed at the Screening and the Primary Outcome/Withdrawal Visits 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.

[*Country-specific Protocol Amendment 1 for UK:*

y S-βhCG pregnancy test should be performed at the Screening and the Primary Outcome/Withdrawal Visits for women of childbearing potential. Urine pregnancy test should be performed at Baseline 1 (Visit 2), Visit 5, Baseline 2 (Visit 6) and Visit 9 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.]

Table of Contents

Appendices

List of Panels

List of Abbreviations and Definitions of Terms

γGT	γ-glutamyl transferase
AE	adverse events
ALT	alanine aminotransferase
AME	absorption, metabolism and excretion
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BACS	Brief Assessment of Cognition in Schizophrenia
BMI	body mass index
bpm	beats per minute
BUN	blood urea nitrogen
CGI-S	Clinical Global Impression – Severity of Illness
CHMP	Committee for Medicinal Products for Human Use (European Union)
CI	confidence interval
CIOMS-I	Suspect Adverse Reaction Report Form of the Council for International Organizations of Medical Sciences
C_{max}	maximum observed concentration
CNV	copy number variation
CPK	S-creatine phosphokinase
CRA	clinical research associate
CRF	case report form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450 isoenzyme
DAI-10	Drug Attitude Inventory - 10
DNA	deoxyribonucleic acid
DSM-5™	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
eCRF	electronic case report form
ED	early-in-disease
EEG	electroencephalogram
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	full-analysis set
FDA	Food and Drug Administration
FIH	first in human
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin

HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IDT	infectious disease testing
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug Application
IRB	institutional review board
I-TMF	investigator trial master file
IVRS	interactive voice response system
LD	late-in-disease
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LLOQ	lower limit of quantification
Lu	Lundbeck
MAD	multiple ascending dose
MD	medical doctor
MINI	Mini International Neuropsychiatric Interview for Psychotic Disorders Studies
MMRM	mixed model for repeated measurements
mRNA	messenger ribonucleic acid
NA	not applicable
NSA-16	Negative Symptom Assessment - 16
NSAIDS	non-steroidal anti-inflammatory drugs
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PBMC	peripheral blood mononuclear cell
PBO	Placebo
PCR	polymerase chain reaction
PCS	potentially clinically significant
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
PR	specific ECG interval describing atrioventricular conduction
PRO	patient-reported outcome
PSP	Personal and Social Performance Scale

QP	qualified person
qPCR	quantitative polymerase chain reaction
QRS	specific ECG interval describing ventricular depolarization
QT	specific ECG interval describing ventricular depolarization/repolarization
QT_c	heart-rate corrected QT interval
QT_{cF}	heart-rate corrected QT interval using Fridericia's correction formula
QT_{cI}	heart-rate corrected QT interval, individually corrected
REML	restricted-maximum-likelihood
RR	specific ECG interval describing the ventricular depolarization/repolarization cycle
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SNP	single-nucleotide polymorphism
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SWN-S	Subjective Well-Being under Neuroleptic Treatment
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed concentration
TMF	trial master file
TRS	treatment resistant schizophrenia
US FDA	United States Food and Drug Administration

1 Introduction

1.1 Background

1.1.1 Overview

Lu AF35700 is a novel compound with affinity for serotonergic, dopaminergic, and α-adrenergic receptors, and acts as an antagonist of those receptor types. Lu AF35700 has a novel pharmacological profile compared to existing therapies. Lu AF35700 is a potential antipsychotic drug in development by H. Lundbeck A/S for the proposed indication of treatment-resistant schizophrenia (TRS) as a once daily tablet formulation.

1.1.2 Schizophrenia

Schizophrenia is a severe, complex, chronic, and disabling psychiatric disorder with a substantial impact on day-to-day functioning and an estimated lifetime prevalence of 0.3 to 0.7%.[1]

Schizophrenia is characterized 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 disorganized 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). Schizophrenia is among the world's most disabling conditions among people in developed countries and is frequently associated with a high degree of social burden as well as great suffering to afflicted individuals and those who care for them.[2] The seriousness of this condition is also reflected by the average reduction in life expectancy of 25 years among people with schizophrenia compared to that in the general population; often as a result of personal neglect, poverty, or suicide.[3]

Schizophrenia is a treatable condition with several therapeutic alternatives available. However, despite advances in the pharmacotherapy of schizophrenia, managing the lack of adequate response to antipsychotic drug treatment remains a great unmet medical need. It has been estimated that one-fifth to one-third of patients with schizophrenia experience persistent symptoms including significant levels of positive symptoms despite several treatment trials and may be classified as being resistant to treatment.[4,5,6,7,8] The treatment of these patients has remained a persistent public health challenge, since they often have a decreased social functioning and a low quality of life, and their treatment is related to high overall costs and increased healthcare resources use.[9]

The following sections provide a brief overview of the nonclinical and clinical data currently available for Lu AF35700. Refer to the current version of the *Investigator's Brochure* for more detailed information.[10]

1.1.3 Nonclinical Data

1.1.3.1 Primary Pharmacology

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 potent binding of Lu AF35700 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, 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.

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*.

1.1.3.2 Toxicology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Toxicologically significant effects were observed only at exposures that were sufficiently in excess of the expected human exposures at a daily dose of 10 mg, indicating that these effects were limited or of no relevance to clinical use.

In dogs, the cardiovascular system was identified as the main target organ system. ECG waveform morphology changes (junctional escape beats and supraventricular ectopic beats) were observed in a cardiovascular safety pharmacology study and in a 4-week oral toxicity study. QT_c-prolongation was observed in a 13-week oral toxicity study, but no ECG changes were observed in the 39-week oral toxicity study. Although the observed changes in QT_c interval cannot be clearly attributed to treatment, a drug related effect cannot be excluded.

The carcinogenic potential of Lu AF35700 is currently being investigated.

In conclusion Lu AF35700 was found to be safe and well tolerated at clinically relevant exposure levels. Please see the current version of the *Investigator's Brochure* for more detailed information.[10]

1.1.4 Clinical Data

1.1.4.1 Overview - Clinical Studies

Currently, four studies with Lu AF35700 have been completed in healthy subjects (studies 14198A, 15867A, 15868A, and 16156A). Two studies in patients with schizophrenia studies

14754A and 15859A) have been completed. The completed studies in healthy subjects (all men) comprise the first-in-human (FIH) study (14198A), an absorption, metabolism, and excretion (AME) study (15867A), a single-dose PET study (PET SD) (15868A), and a pharmacokinetic (PK) study (16156A) in Japanese and Caucasian subjects (PK JAPAN).

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 SD studies, 6 subjects received a single dose of 30 mg Lu AF35700. The PK JAPAN study consisted of three parts: Part A, in which 12 Japanese and 12 Caucasian men received a single dose of 5 mg Lu AF35700; Part B, in which 12 Japanese men received a single dose of 10 mg Lu AF35700; and Part C, in which 12 Japanese and 12 Caucasian men received a dose of 10 mg/day Lu AF35700 for 5 days. No serious adverse events have been reported in healthy subjects and the majority of adverse events related to the treatment have been mild. Based on these studies, Lu AF35700 was safe and well tolerated by healthy subjects. Please see the *Investigator's Brochure* for more detailed information.[10]

Multiple daily doses of Lu AF35700 in the dose range of 5 to 30 mg/day for up to 21 days have been administered in a multiple ascending dose (MAD) study (14754A) with a total of 70 male and female patients and a PET (PET MD) study (15859A) in 22 male patients with schizophrenia. In the MAD study, there was no difference in tolerability and safety with respect to sex (men versus women). In addition, in the MAD study, doses of 45 and 75 mg have been administered on Study Days 7 and 14 after 6 days of daily dose titration to the same patient population. The daily and the weekly dosing regimens were safe and well tolerated by the patients with schizophrenia.

Currently three studies are ongoing; one pivotal study in patients with treatment resistant schizophrenia (TRS1, Study 16159A), an open label safety extension study to TRS1 (Study 16159B), and a dedicated ECG study in patient with schizophrenia (Study 16323A). As of November 2016, a total of 83 healthy subjects and 96 patients with schizophrenia have been exposed to Lu AF35700 and 36 patients with TRS have been exposed to Lu AF35700 or risperidone/olanzapine.

1.1.4.2 Pharmacokinetics

1.1.4.2.1 Pharmacokinetics of Lu AF35700 and Lu AF36152

The exposure of Lu AF35700 and the metabolite Lu AF36152 appears to be dose proportional in the dose range investigated and there do not seem to be a difference in the PK parameters between healthy subjects and patients with schizophrenia.

Preliminary data points to about 35% lower exposure after oral tablet administration compared to that after oral solution administration. Comparing 4 fasting and 5 fed patients receiving the tablet formulation showed that the exposure of Lu AF35700, as assessed by AUC_{0-72} and C_{max} was 22% and 11% higher, respectively, in the fed state compared to the

fasted state. No difference in t_{max} was observed between dietary states, therefore administration of Lu AF35700 can be made irrespective of meals.

The variability across the PK parameters is moderate to high for all PK parameters.

Please refer to the *Investigator's Brochure* for a summary of PK parameters.[10]

1.1.4.2.2 Population Pharmacokinetic Analysis

An initial pooled integrated popPK analysis for Lu AF35700 and Lu AF36152 was performed on data from 7 studies.[11]

The absorption was described as slow and extended giving average t_{max} of Lu AF35700 of 9 hours and 14 hours for Lu AF36152. Large volumes of distribution (~5000L) of Lu AF35700 and Lu AF36152 were estimated implying extensive distribution to peripheral tissue. Inferred metabolic status of CYP2C19 was found to affect the oral clearance of Lu AF35700.

There was no consistent trend for a correlation between CYP2D6 inferred metabolic status and oral clearance for Lu AF35700. A relation between oral clearance of Lu AF36152 and the CYP2D6 inferred metabolic status was found. Oral clearance of Lu AF36152 was found to increase with increasing creatinine clearance.

The pharmacokinetics of Lu AF35700 and Lu AF36152 were similar in healthy subjects and schizophrenic patients.

From the population estimates, the elimination half-life for Lu AF35700 and Lu AF36152 was estimated to 153 hours and 249 hours, respectively.

1.1.4.3 Safety and Tolerability

The main body of safety data in patients with schizophrenia comes from the MAD study (70 patients, Study 14754A). The safety data from the FIH, AME, and single-dose PET studies in healthy subjects and the multiple dose PET study in patients show a benign safety profile similar to that in the MAD study, but the total number of subjects and exposure with Lu AF35700 in those studies is small compared to the MAD study.

The total number of healthy subjects (83) who have received Lu AF35700 is slightly lower than that for patients (132 in total; with 36 of the 132 patients with schizophrenia still blinded and randomized to either Lu AF35700 or risperidone/olanzapine) 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.

In the MAD study, the adverse events with the highest incidence (>10%) in the Lu AF35700 groups in the daily dosing cohorts were reported to be: 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 of 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.

Based on safety and tolerability data from the FIH, single-dose PET, AME, and PK JAPAN studies in healthy subjects (Studies 14198A, 15868A, 15867A, and 16156A, respectively), a single dose of up to 30 mg Lu AF35700 was safe and well tolerated. Furthermore, in the MAD and MD PET studies in patients with schizophrenia (Studies 14754A and 15859A, respectively), multiple doses in the dose range 5 to 30 mg/day or 45 or 75 mg once weekly for 21 days, were safe and well tolerated.

1.1.4.4 Target Occupancy

The multiple dose Lu AF35700 PET study (15859A) was conducted in 22 male patients with schizophrenia to characterize the relationship between plasma concentration of Lu AF35700 and Lu AF36152 and the D_1, D_2 and 5-HT_6 receptor occupancy. For the D_1 receptor in the caudate nucleus, putamen, and ventral striatum, three weeks of 10 mg/day resulted in maximum receptor occupancy levels of 88, 83 and 82%, respectively. For the D_2 receptor in the caudate nucleus, putamen, and ventral striatum, three weeks of 20 mg/day resulted in maximum receptor occupancy levels of 67, 65 and 64%, respectively. For the 5-HT_6 receptor in the caudate nucleus, putamen and ventral striatum, three weeks of 10 mg/day resulted in maximum receptor occupancy levels of 94, 90 and 88%, respectively.[12]

For all three receptors, the relationships between plasma concentration of Lu AF35700 and LuAF36152 and receptor occupancy (mean occupancy from caudate nucleus, putamen, and ventral striatum) could be described be E_{max} models. Daily doses of 10 mg are predicted to result in mean D_1, D_2 and 5-HT_6 occupancy levels of 74, 43 and 87%, respectively, at steady state of Lu AF35700 and Lu AF36152.[13]

1.2 Rationale for the Study

The current study is a Phase III study included in the Lu AF35700 clinical development programme of Lu AF35700 as a potential treatment of treatment-resistant schizophrenia (TRS). The design was adopted from TRS1 (Study 16159A) and the dose was partly based on the PET MD study results. Targeted enrolment and stratification of patients with ED TRS and LD TRS, as defined in this protocol, may increase the understanding of how Lu AF35700 may be an effective treatment across the longitudinal course of disease.

Clinical studies present an excellent opportunity for collecting large numbers of biological samples from well-characterized 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 future potential 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 assess the efficacy of Lu AF35700 on symptoms of schizophrenia in patients with early-in-disease (ED) or late-in-disease (LD) treatment–resistant schizophrenia (TRS)

Secondary Objectives

- to assess the efficacy of Lu AF35700 on symptoms of schizophrenia in patients with ED TRS
- to assess the efficacy of Lu AF35700 on negative symptoms of schizophrenia in patients with ED or LD TRS

Exploratory Objectives

- to assess the efficacy of Lu AF35700 in patients with ED TRS *versus* patients with LD TRS
- to assess the efficacy of Lu AF35700 in patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit *versus* patients with LD TRS
- to assess the efficacy of Lu AF35700 in patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
- to assess the effect of Lu AF35700 on cognitive performance and functioning in patients with ED TRS, LD TRS, or patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
- to explore patient historical and demographic characteristics predictive of response to treatment with Lu AF35700
- to explore genetic markers (genotype and expression) predictive of, or associated with, response to treatment with Lu AF35700

Safety Objective

- to evaluate the safety and tolerability of Lu AF35700 in patients with ED or LD TRS

3 Study Design

3.1 Overview of the Study Design

This study has been designed in accordance with the *Declaration of Helsinki.*[14]

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

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[15] and applicable regulatory requirements.

An overview of the study is presented in Panel 1.

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

Patients to be enrolled in the current study should fulfil either the criteria for ED TRS or LD TRS.

The study is planned to include patients from US, Europe, Japan, or South America. In total, 490 patients in US, Europe, Japan, or South America are planned for randomization with 245 randomized patients per treatment group.

The total study duration per patient from Screening to the end of Follow-up will be 23 weeks (including 3 weeks screening period) For patients enrolling in the separate open-label extension study, the corresponding total study duration is 17 weeks (excluding the safety follow-up period).

The study will consist of 4 Periods:

- Screening Period (up to 3 weeks)
- Period A – Prospective Confirmation Period (6 weeks)
- Period B – Double-blind Treatment Period (8 weeks)
- Safety Follow-Up Period (6 weeks) – as applicable

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

In this study patients are blinded to any transition in care from Period A to Period B; specifically, the patients are kept blinded to the time point of randomization at Baseline 2 and to the treatment that they may receive during this study. In addition, patients must remain blinded to any association with their response to the treatment and their continuation in the study.

Patients, who meet the pre-specified selection criteria for either ED or LD TRS, will enter a single (patient)-blinded treatment period with risperidone or olanzapine to confirm their resistance to antipsychotic drug treatment.

Current antipsychotic drug treatment will be down-tapered within the first 7 days of Period A as described in section 6.1. Patients currently treated with depot antipsychotics can, after signing the ICF, be down-tapered by skipping one full treatment cycle plus 3 days before 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 or in a documented treatment failure in the past 2 years, or have a documented history of intolerance to risperidone (or 9-hydroxy-risperidone; Invega™) treatment in the past 2 years, 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. For patients treated with risperidone or Invega™ more than 2 years ago and for whom the treatment resulted in an inadequate response or intolerance to the treatment, the investigator may consult with Lundbeck and/or its designee whether such patients may receive olanzapine; this decision must be approved by Lundbeck and/or designee. Thereafter, the dose of olanzapine may be adjusted up once from 15 to 20 mg/day during Weeks 3 and 4, for efficacy according to the investigator's clinical judgement. If necessary for tolerability, dose may be decreased once back to 4 mg/day risperidone, or 15 mg/day olanzapine, during Weeks 3 and 4. No dose adjustments are allowed during the last 2 weeks of Period A (Weeks 5 and 6).

Patients who do not fulfil the inclusion criteria for Period B (blinded to site and patient) will be withdrawn from the study.

Patients who fulfil the entry criteria for Period B will enter the double-blind treatment period at Baseline 2. The specific inclusion criteria for Period B will be blinded to the site and patient. Patients will be randomly assigned (1:1) to 8 weeks of double-blind treatment with either Lu AF35700 (10 mg/day) or to continue the treatment with risperidone or olanzapine at a dose set at the end of Week 4 (Visit 5) of Period A. The randomization will be stratified by duration of disease (early-in-disease and late-in-disease). Patients with ED and LD TRS will be enrolled such that an approximate 1:2 ratio is achieved.

For patients randomized to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion during the initial 7 days of Period B. The dose of Lu AF35700, risperidone or olanzapine will be fixed throughout Period B (Lu AF35700: 10 mg/day; risperidone: 4 mg/day or 6 mg/day, determined in Period A; olanzapine: 15 mg/day or 20 mg/day, as determined in Period A).

All patients, study completers, and those who prematurely discontinue will be scheduled for a Safety Follow-up Visit for safety assessments 6 weeks after the last dose of IMP, with the exception of those patients entering the open-label extension study.

Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will, in addition to the Withdrawal Visit, be asked to attend an Efficacy Follow-up Visit (Visit 13), for the assessment of efficacy, safety and concomitant medication. This visit coinciding with the time point of the Primary Outcome Visit (Week 14) that should have taken place, had the patient not been withdrawn from the study.

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.

Patients who complete or withdraw from the study should be treated according to current clinical practise at the discretion of the investigator.

3.2 Rationale for the Study Design

The randomized, double-blind, active-controlled, fixed dose design of the study aims to evaluate the safety and efficacy of Lu AF35700 on symptoms of schizophrenia in patients with ED TRS or LD TRS. Targeted enrolment and stratification of patients with ED TRS and LD TRS, as defined in this protocol, may increase the understanding of how Lu AF35700 may be an effective treatment across the longitudinal course of disease. The criteria used to define treatment-resistance in this study are failure to respond after two trials of antipsychotic drug treatment of adequate dose and duration of at least 6 weeks.[16] 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 8, 9 and 10, as well as persistent illness and drug-resistant condition as defined by exclusion criterion 13. The second failed antipsychotic trial will be prospectively documented in Period A of this study. The rationale for considering two failed trials as sufficient evidence of TRS is supported by the finding that patients not responding to two adequate antipsychotic trials have less than 7% chance of responding to another trial;[17] a criterion which has been broadly adapted in recent TRS studies.[18]

Patients entering Period B will be randomized to continue treatment with risperidone or olanzapine or to treatment with one dose (10 mg daily) 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. The blinding of the investigators to the randomization criteria at the end of Period A is designed to further reduce possible sources of bias in the assessment of efficacy in patients with TRS.

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 minimizing bias. The primary analysis assumes data are missing at random. As sensitivity analysis, this assumption will be investigated by utilizing the retrieved dropout data from the Efficacy Follow-up Visit.

The doses of risperidone and olanzapine used in this study are known to be safe, effective and well-tolerated.[19] The 10 mg doses of Lu AF35700 was determined to be safe and well tolerated in the Phase I programme in patients with schizophrenia and elicited the targeted range of D_2 receptor occupancy in healthy subjects (see *Investigator's Brochure)*.[10] The treatment duration of 8 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.[10]

Efficacy and predictors of response to treatment will be assessed using:

- PANSS,[20] a well established scale for assessing severity of the symptoms of schizophrenia.
- CGI-S,[21,22] a global measure of outcome,
- NSA-16,[23] a validated rating of the severity of the negative symptoms of schizophrenia
- PSP,[24] a validated rating for functional outcome in schizophrenia
- BACS,[25,26] a validated assessment of cognitive function in schizophrenia
- SWN-S[27] and DAI-10,[28] both validated patient reported outcomes of studies in schizophrenia
- historical and demographic characteristics of the patient's illness that may provide predictors of response to treatment

In addition, genetic markers will be assessed that may aid in understanding the risk associated with the development of TRS.

Safety and tolerability will be assessed by means of withdrawal, reported adverse events, vitals signs, weight, clinical safety laboratory tests, ECGs, physical examinations and C-SSRS.

Metabolic adverse events including body weight gain, dyslipidemia, and hyperglycemia are adverse events associated with antipsychotic drug treatment and represent an important long-term safety risk.[29] 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.

Blood samples will be collected to further understand the pharmacokinetic properties of Lu AF35700 and its metabolite (Lu AF36152), as well as to risperidone (including 9-hydroxy-risperidone and olanzapine) and to explore genetic markers that my aid in understanding the risk associated with the development of TRS.

4 Ethics

4.1 Ethical Rationale

This study will be conducted in compliance with the principles of *Good Clinical Practice*.[15]

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.

Targeted enrolment and stratification of patients with ED TRS and LD TRS, as defined in this protocol, may increase the understanding of how Lu AF35700 may be an effective treatment across the longitudinal course of disease.

Given the unique receptor binding profile of Lu AF35700 characterized by a high affinity to dopamine D_1 and serotonin 5-HT_6 receptors combined with a low level of dopamine D_2 interaction, Lu AF35700 has the potential to offer an effective alternative treatment option for patients with TRS.

Based on data from the ongoing clinical pharmacology programme in patients with schizophrenia, the dose used in the current study is considered to be safe and well tolerated.

The aim of this study is to generate supporting evidence for efficacy and safety of Lu AF35700 in patients with TRS. 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 recommendations provided for conducting studies inpatients with TRS as outlined in the EMA guideline on clinical investigation of medicinal products, including depot preparations, in the treatment of schizophrenia.[14,30]

In the current study, eligible patients who have had a recent treatment failure will enter a single (patient) blind confirmation period and initiate a treatment trial with risperidone or olanzapine (well-known and widely used antipsychotic drugs), to assess treatment response. Only patients where a lack of adequate treatment response is confirmed will be randomized to double-blind treatment with either Lu AF35700 or to continued treatment (risperidone or olanzapine) for a period of 8 weeks. Patients who respond to the initial treatment with risperidone or olanzapine will be excluded from the study. Thus, approximately half of the non-responding patients will be randomized back to the failed treatment used in the initial period of the current study. This study design is considered ethically justifiable given the limited treatment options for this patient population and the need to utilize a rigorous scientific design to develop new safe and effective treatments for TRS.[31,32] Blinding of the patients and of the investigators, as described in the study design, to actual treatment received reduces bias that would otherwise be introduced and that may influence the reliability of the study results.

The duration of the double-blind treatment period in the current study is 8 weeks in order to provide sufficient time to determine the extent of attainable symptom reduction and allow safety evaluation. In general, an adequate treatment trial in TRS should have a minimum duration of 6 weeks[33]. The 8-week duration in this study further allows adequate time for patients to receive Lu AF35700 under steady state conditions while their response is being assessed. 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. Patients who complete the study will be offered to continue in an optional

52-week, open-label extension study (Study 17303B) if eligible according to the selection criteria for that study. All patients enrolled in the current study (Study 17303A) who do not continue in Study 17303B will be scheduled for a Safety Follow-up Visit 6 weeks after last dose of IMP.

Blood samples will be collected for in study and possible use in future exploratory research study(ies) in an attempt to increase the understanding of the properties of Lu AF35700, aetiology of schizophrenia, and the molecular basis of drug response.

In accordance with *Good Clinical Practice*,[15] qualified medical personnel at CRO or 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.

In accordance with *Good Clinical Practice*,[15] the investigator will be responsible for all study-related medical decisions.

The total volume of blood drawn from each patient will not exceed 250 mL, and is not considered to pose any risk or significant discomfort to the patients.

Based on the above-mentioned considerations the potential risk of participating in the study is well managed by the study set-up and considered negligible.

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.

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 the aims, methods, and potential hazards of the study and any discomfort it may entail.

The patients 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
- of the possibility of withdrawing consent (section 8.4)
- that they have the right to request a copy of their personal data from the study via the investigator
- after the study has been reported, that they have the right to be informed by the investigator about which treatment they received
- about their right to receive information about the study results from the investigator on the patients' own initiative; the results will be available approximately 1 year after the end of the study

The patients must be informed that persons authorized by Lundbeck and authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ethics committees (ECs) or institutional review boards (IRBs)) may view their medical records. The patients must also be informed that de-personalized copies of certain parts of the patients' medical records may be requested by authorized personnel from certain authorities (domestic, foreign, data protection agencies, or ECs or IRBs) for verification of study procedures and/or data. The confidentiality of the patients will in all cases be respected.

The patients 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. Prior to including a patient in the study, an *Informed Consent Form* must be signed and dated by the patient and signed and dated by the investigator or a designee. The patients 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 separate *Patient Information Sheet* and a *Material Transfer Agreement*.

A patient may, at any time and without stating a reason, specifically request the destruction of the patient's DNA or PBMC sample, irrespective of the patient's 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 or designee when the sample has been destroyed.

Listing of all potential *Informed Consent Forms* (ICFs):

- The study ICF covers all study assessment, including but not limited to, CYP genotyping, gene expression profiling (RNA), metabolomics/proteomics and the optional in-study pharmacogenetics
- Pharmacogenetics biobank sampling ICF (optional)
- If applicable: Partner Pregnancy ICF (see section 10.2).

4.3 Personal Data Protection

The data collected in this study will be processed in accordance with the specifications outlined in the Danish Data Protection Act and in the European Union legislation[34] to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organization to ensure compliance with the above-mentioned legislation.

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 IECs /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 Lundbeck has received confirmation that written approval of the protocol has been granted by the appropriate IEC or IRB.

The investigator must not allow any patients to participate in the study 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 written approval must be obtained before implementation of the amendment, if required by local law.

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.

This study will be conducted only after Lundbeck has received confirmation that written approval or confirmation of notification has been received from the regulatory authorities.

5 Study Population

5.1 Numbers of Patients and Sites

Planned regions: US, Europe, Japan, and South America

Approximately planned number of patients:

to be screened (with signed informed consent):	1262
to be included-in Period A:	817
to be randomized:	490
to complete the treatment period:	392

Approximately planned number of:

study sites:	100

The number of enrolled patients is based on an assumed attrition rate of 40% in Period A and may be adjusted to meet the target of 490 randomized patients.

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 are randomized 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. In order to achieve the planned stratification of patients with ED and LD TRS randomized in Period B, the sponsor may instruct a given site, from time to time, to specifically and exclusively enrol patients with either ED or LD TRS. The stratification will be monitored by the IVRS system.

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 is able to read and understand the *Informed Consent Form*.
3. The patient has 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 receiving treatment with a psychiatrist in either an inpatient or outpatient facility.
6. The patient has schizophrenia, first diagnosed <10 years OR ≥10 years prior to the Screening Visit and according to DSM-5™ and confirmed by the Mini International Neuropsychiatric Interview (MINI).
7. The patient has been treated with adequate dose(s) of antipsychotic drug treatment for at least 2 weeks prior to the Screening Visit.
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 drug prescribed for an adequate time (at least lasting for 6 weeks) within 2 years prior to the ScreeningVisit. The failure to respond to the current antipsychotic drug treatment trial may be considered a retrospective failed treatment, if the patient has been treated for 6 weeks with adequate dose(s) of antipsychotic drug(s).
9. The patient has a PANSS total score of ≥80 (on 1-7 scale) and a score of ≥4 (≥ "Moderate" on 1-7 scale) on at least 2 of the following PANSS items (at the Screening and at the Baseline 1 [Week 0] Visits):
   - P2 - Conceptual disorganization
   - P3 - Hallucinatory behavior
   - P6 - Suspiciousness/persecution
   - G9 - Unusual thought content
10. The patient has a CGI-S score of ≥4 (≥ "Moderately ill") at the Screening and at the Baseline 1 [Week 0] Visits.
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 him/herself 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, intrauterine devices, sexual abstinence[1], 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 sterilized 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 defined as a combination of male condom and female using an adequate, highly effective contraception; this combination of contraceptive methods must be used from the Baseline 1 Visit to ≥3 months after the last dose of IMP, OR have been surgically sterilized prior to the Screening Visit

Entry criteria Period B

16. The patient has completed Period A of the study.
17. Response criteria, blinded to site and patient and described in the *Clinical Study Protocol Addendum- Unmasked Information*, are satisfied.
18. Patient is considered to have been adherent with assigned IMP in Period A. Adherence is assumed based upon taking at least 80% of assigned IMP during Period A.
19. The patient's designation as ED TRS or LD TRS does not invalidate the *a priori* specified stratification plan for patients randomized into Period B

Exclusion Criteria

General

1. The patient has previously been screened in this study or has received Lu AF35700.
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.

[1] *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject*.]

4. Not applicable (Criterion removed in Protocol Amendment 2)
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.
11. The patient suffers from mental retardation, 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 symptom relief corresponding to a CGI-S score of 3 (mild) or less as a result of antipsychotic drug treatment during the majority of time in the 2-year period prior to the Screening Visit.
14. The patient has a current diagnosis or a history of substance use disorder according to DSM-5™ criteria within 6 months prior to the Screening Visit with the exception of tobacco, or mild cannabis or mild alcohol use disorder. Patients with a positive drug screen test, with the exception of cannabis and verified by repeated testing, are excluded from the study.
15. The patient is at significant risk of harming himself/herself or others according to the investigator's judgement, or the patient on the C-SSRS:
    - Answers "Yes" to questions 4 or 5 on the Suicidal Ideation section within the last 3 months at the Screening Visit, OR
    - Answers "Yes" to any question on the Suicidal Behaviour section within the last 3 months at the Screening Visit, OR
    - Answers "Yes" to questions 4 or 5 on the on the Suicidal Ideation section at the Baseline 1 Visit
16. The patient has started formal cognitive or behavioural therapy or systematic psychotherapy within 6 weeks prior to the Screening Visit, or plans to start such therapy during the study. Any on-going formal psychotherapy initiated more than 6 weeks prior to the Screening Visit 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
19. The patient has received electroconvulsive therapy <6 months prior to the Screening Visit.

Medical

20. 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.
21. 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.
22. The patient has epilepsy or a history of seizures, except for a single seizure episode (for example, childhood febrile seizure, post traumatic, or alcohol withdrawal).
23. 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
24. The patient has clinically significant abnormal vital signs at the Screening Visit.
25. 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 one of the following:
    - 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

26. The patient has, at the Screening Visit, one of the following:
    - inadequately controlled diabetes or receives diabetes treatment, which is not considered stable in the investigator's opinion
    - an HbA1C value >8%
    - in <12 months prior to Screening Visit experienced severe hypoglycaemia (according to American Diabetic Association criteria) OR has been hospitalized for ketoacidosis
27. The patient has orthostatic hypotension (defined as a decrease in systolic blood pressure >20 mmHg measured first in the supine or sitting position and then 1 to 3 minutes thereafter in the standing position) that is considered clinically relevant by the investigator.
28. The patient has, at the Screening Visit one of the following:
    - an abnormal ECG that is, in the investigator's opinion, clinically significant
    - a PR interval >250 ms
    - a QRS interval >130 ms
    - a QT_{cF} interval >450 ms (for men) or >470 ms (for women) (based on the Fridericia correction where $QT_{cF} = QT/RR^{0.33}$)
29. 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 withdraws his or her consent (defined as a patient who explicitly takes back his or her consent); section 8.4 states how the patient's data will be handled.
- the patient is lost to follow-up (defined as a patient who fails to comply with scheduled study visits or contact, who has not actively withdrawn from the study, and for whom no alternative contact information is available [this implies that at least two documented attempts have been made to contact the patient]).

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 from treatment
- any site personnel break the randomization code for that patient
- the patient becomes pregnant
- the patient has a critical value of prolactin >250ng/mL (>5285mUI/mL)
- 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 the Screening Visit 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 that identifies substance use that jeopardizes patient safety or the reliability and integrity of the study protocol 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 the patient 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

A patient may be withdrawn from the study if:

- the patient fails to comply with study procedures

Patients who withdraw will not be replaced.

6 Investigational Medicinal Products (IMPs)

6.1 Treatment Regimen

Patients, who meet the pre-specified selection criteria for either ED or LD TRS, will enter a single (patient)-blinded treatment period with risperidone[35] or olanzapine[36] to confirm resistance to antipsychotic drug treatment.

Period A - Prospective Treatment Period

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-hydroxi-risperidone; Invega™) in the most recent treatment trial, or in a documented treatment failure in the past 2 years, or have a documented history of intolerance to risperidone (or 9-hydroxy-risperidone; Invega™) treatment in the past 2 years, 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. 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. If necessary for tolerability, the dose may be decreased once back to 4 mg/day during Weeks 3 and 4. The dose must not be adjusted during Weeks 5 and 6.
- Olanzapine: 5 mg/day for the first 2 days; then, 10 mg/day for the next 2 days; then 15 mg/day for the last 3 days. The dose may be increased once to 20 mg/day during Weeks 3 and 4. If necessary for tolerability, the dose may be decreased once back to 15 mg/day during Weeks 3 and 4. The dose must not be adjusted during Weeks 5 and 6.

The last possible time point for dose adjustment is at Visit 5.

For patients treated with risperidone or Invega™ more than 2 years ago and for whom the treatment resulted in an inadequate response or intolerance to the treatment, the investigator may consult with Lundbeck and/or its designee whether such patients may receive olanzapine; this decision must be approved by Lundbeck and/or designee. Current antipsychotic drug treatment will be down-tapered within the first 7 days of Period A. Patients currently treated with 'depot' antipsychotics 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 (blinded to site and patient) will be withdrawn from the study.

Period B - Double-blind Treatment Period

Patients who fulfil the entry criteria Period B will enter the double-blind treatment Period (Period B) at Baseline 2. The specific inclusion criteria for Period B will be blinded to the site and patient. Patients will be randomly assigned (1:1) to 8 weeks of double-blind treatment with either Lu AF35700 (10 mg/day) or to continue the treatment with risperidone or olanzapine at a dose set at the end of Week 4 (Visit 5) of Period A. The randomization will be stratified by duration of disease (ED and LD). Patients with ED TRS or LD TRS will be enrolled such that an approximate 1:2 ratio is achieved.

The dose of Lu AF35700, risperidone or olanzapine will be fixed throughout Period B (Lu AF35700: 10 mg/day; risperidone: 4 mg/day or 6 mg/day, determined in Period A; olanzapine: 15 mg/day or 20 mg/day, as determined in Period A). For patients randomized to Lu AF35700, discontinuation of risperidone or olanzapine will be done gradually in a blinded fashion during the initial 7 days of Period B 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

Discontinuation of IMP

Discontinuation of IMP will be initiated at the Primary Outcome or Withdrawal Visit for all patients who discontinue the study for any reason after Week 1 of Period A or anytime during Period B. The investigator has the option to discontinue IMP through down-titration (recommended) or to stop IMP abruptly for safety or tolerability issues. Down-titration proceed according to the following scheme:

- Risperidone (4 mg/day): 2 mg/day for the first 4 days; placebo for the 3 subsequent days
- Risperidone (6 mg/day): 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

Discontinuation of IMP during the first week of Period A will be abrupt.

IMP Intake

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 based on patients' preference. The capsules are to be swallowed whole. The first dose is to be taken the day after IMP has been dispensed to the patient at Baseline 1. Administration of IMP can be made irrespective of meals.

If the investigator during the study for tolerability reasons decides to switch a patient´s dosing schedule from taking the capsules in the evening to taking the capsules in the morning, it is accepted that IMP intake is skipped for one day.

6.2 IMPs, Formulations, and Strengths

The IMPs supplied by Lundbeck in this study are:

- Lu AF35700 – 10 mg/day; encapsulated tablets
- Risperidone – 2, 4, and 6 mg/day, encapsulated tablets
- Olanzapine – 5, 10, 15, and 20 mg/day, encapsulated tablets
- Placebo – encapsulated tablets

The IMPs will be identical in appearance.

6.3 Manufacturing, Packaging, Labelling, and Storage of IMPs

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

The IMP will be provided in wallet cards 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.

6.4 Method of Assigning Patients to Treatment

Each patient will be assigned a screening number by the eCRF system, and that number will be used to identify that patient throughout the study.

An interactive voice response system (IVRS) will be used in this study. When a patient is to be enrolled and randomized, the investigator will contact the IVRS. The IVRS will allocate the patient to a treatment group during the call, and at the Baseline 2 Visit assign the patient a randomization number in accordance with the specifications from Biostatistics, H. Lundbeck A/S, and then follow up by fax, e-mail, or the web (depending on availability or preference at the site).

Separate randomization lists have been prepared, one for US/Europe/South America and one for Japan.

6.5 IMP Accountability

The IMP accountability must be documented at each site:

- site-specific log to track the complete inventory (that is, what is shipped between the site and Lundbeck)
- 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 IMPs to patients enrolled in the study. The investigator or the pharmacist (if applicable) must maintain an adequate record of the receipt and distribution of the IMPs. This record must be available for inspection at any time.

6.6 Unblinding Procedures

Pharmacovigilance, H. Lundbeck A/S, and the investigator or the pharmacist (if applicable), will have access to the unblinded information for 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 for a patient if knowledge of the IMP is necessary to provide optimal treatment to the patient in an emergency situation. If possible, the investigator should consult the CRA before breaking the code. The investigator must record the date and reason for breaking the code on the *IMP Code Break Form* in the eCRF. 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 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. When the code is broken for a patient, the

patient must be immediately withdrawn from the study. If this occurs during a visit, the investigator must complete the visit as a Withdrawal Visit; otherwise, the patient will be asked to attend a Withdrawal Visit.

6.7 Post-study Access to IMPs

Patients who completed treatment until Visit 11 (Primary Outcome) may continue into an optional 52-week open-label extension study (Study 17303B), if informed consent is obtained and the patient is eligible per Study 17303B eligibility criteria. Patients who do not continue into the extension study, or withdraw from this study, should be treated according to current clinical practice at the discretion of the investigator.

7 Concomitant and Rescue Medication

7.1 Concomitant Medication

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

The recent and concomitant medications that are disallowed or allowed with restrictions during the study are summarized 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 initiated after the last dose of IMP must only be recorded if associated with an SAE or an ongoing AE.

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.[35,36] Examples of inhibitors and inducers are provided in Appendix II. [*Country-specific Protocol Amendment 1 for JP: Clinicians should use caution when prescribing the concomitant use of CYP3A inhibitors (eg. itoraconazole etc.) with risperidone as there is a risk of increasing blood concentrations of the risperidone parent compound and its metabolites]*.

7.2 Rescue Medication

Guidance on use of rescue medication is outlined in Appendix II and specified for anticholinergics, anxiolytics and hypnotics.

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 treatment the patient must be treated in accordance with usual clinical practice, unless the patient enters the open-label extension study.

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 antipsychotics 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 the eCRF as the Visit Date.

Patients will enter a Screening Period of up to 21 days to assess eligibility. The patient's eligibility will be reviewed by an external or sponsor medical team based on key protocol inclusion and exclusion criteria to promote appropriate patient enrolment and data quality. Sites should submit specific screening information within 72 hours from the Screening Visit for review by external or sponsor medical team prior to proceeding to Baseline 1 Visit.

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.

Only patients with schizophrenia that are resistant to treatment (patients with TRS) can be enrolled in this study. The main criterion to define TRS is a failure to respond to two antipsychotic drug treatment trials of adequate dose and duration. For the purpose of this study, at least one adequate antipsychotic drug treatment failure must be documented anytime in the past 2 years prior to the Screening Visit as described in inclusion criterion 8 (retrospective documentation). The patient's medical records are the most comprehensive source to document antipsychotic treatment failure. Thus, it is required that the investigator attempts to obtain copies of present or previous medical records of psychiatric and general medical history for every patient in order to document treatment failure. 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 drug treatment trial.

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 drug treatment trials in the last two years gathered from all available sources, including psychiatric interview and examination, and discussion with previous treating physician or treatment team. 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 medical monitor 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 will be considered not eligible for the study.

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.

8.2.1 Pre-screening

Each site must record in a pre-screening log which patients attended the Screening Visit. Sites should also record in a log which patients have been pre-screened.

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 and Re-consenting

Re-screening is not allowed in this study.

Patients who have previously signed the *Informed Consent Form* but not completed any other screening assessments may be considered for re-consenting upon discussion with the Medical Expert at Lundbeck. A new screening number will be assigned in the eCRF.

8.3 Baseline 1 Visit (Visit 2)

In exceptional cases, the visit interval between the Screening and Baseline 1 Visits may be extended with consent from the Medical Expert at Lundbeck, provided the Medical Expert accepts the rationale provided for the extension.

The pharmacogenetic sampling should be taken at the Baseline 1 Visit, but may be collected at a later visit including a clinical safety laboratory sample should it be missed.

8.4 Withdrawal Visit

Patients who withdraw from treatment OR 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 from the study, except information collected in relation to the scheduled Withdrawal Visit or Efficacy Follow-up Visit (see section 8.6) needed for the follow-up of adverse events (section 10.5). The reason for withdrawal must be recorded in the eCRF.

For a patient who withdraws consent:

- if the patient withdraws consent during a visit and then agree(s) 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 that visit will be used
- if the patient withdraws 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 that 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 records
- if the patient explicitly requests that the patient's data collected from the time of withdrawal of consent onwards not be used, this will be respected

8.5 Safety Follow-up Visit (Visit 12)

The Safety Follow-up Visit is conducted to capture serious adverse events (SAEs) that occur during the Safety Follow-up Period as well as to follow up on the outcome of adverse events ongoing at the end of the Treatment Period. The safety follow-up may either be conducted as a visit to the site or as a telephone contact. If any new SAEs have occurred since the last assessment at which the patient received IMP, the safety follow-up must, when possible, be a visit to the site. The safety follow-up must be conducted 6 weeks after the last dose of IMP.

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 *Ongoing Adverse Event* checkbox on the *Adverse Event Form* must be ticked. SAEs must be followed until resolution or the outcome is known.

For patients with a clinically significant out-of-range clinical safety laboratory test value at the Primary Outcome or Withdrawal Visit or who withdrew due to an elevated AST or ALT value (see section 5.4), on site safety follow-up visits should be scheduled; see section 10.5 for details.

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

8.6 Efficacy Follow-up Visit (Visit 13)

Patients withdrawn during Period B (except those withdrawing due to withdrawal of consent) will, in addition to the Withdrawal Visit, also be asked to attend an Efficacy Follow-up Visit (Visit 13), for assessment of efficacy, safety and concomitant medication. This visit coincides with the time point of the Primary Outcome Visit (end of week 14) that should have taken place, had the patient not been withdrawn from the study. If patient attends the Withdrawal Visit 5 days prior to week 14 (planned Primary Outcome Visit) the patient should not be asked to come for a Efficacy Follow-up Visit.

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 end of the study is defined as the last protocol-specified contact with the last patient ongoing in the study. 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 and Demographics

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

9.1.2 Other Baseline Characteristics

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

- Diagnosis (DSM-5 ™), including:
  - age at first diagnosis of schizophrenia
- Relevant social, medical and psychiatric history, including:
  - Premorbid Adjustment Scale (only at Baseline 2)
  - estimation of the duration of untreated psychosis
- Disease-specific history including retrospective documentation of treatment failure, including:
  - timeline of previous antipsychotic drug treatment trials with outcomes
  - timeline of symptomatic psychosis
- Alcohol and substance use, past and current
- Family psychiatric history
- Prior antipsychotic and disallowed medication washout (see chapter 7)
- Height without shoes

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

9.1.2.1 Premorbid Adjustment Scale (PAS)

The PAS[37] is a rating scale designed to evaluate the degree of achievement of developmental goals at each of several periods of a subject's life before the onset of schizophrenia (6 months prior to psychiatric symptomatology). The level of functioning evaluated in four major areas, at each of several periods of the subject's life, include: social accessibility- isolation, peer relationships, ability to function outside the nuclear family, and capacity to form intimate socio-sexual ties. Items evaluating age-appropriate functioning in these areas are repeated for each period of the subject's life. The four life period sections are as follows: Childhood, up to 11 years; Early Adolescence, 12-15 years, Late Adolescence, 16-18 years; and Adulthood, 19 years and beyond. The final section, labelled *General*, is more global, containing items meant to estimate the highest level of functioning that the subject achieved before becoming ill, as well as the time span and characteristics of onset of illness, and general information such as amount of education.

Each section of the scale contains a number of items with a scoring range of 0 (hypothetically healthiest) to 6 (hypothetically least healthy). When no information is available for a particular item, the item is not scored. The *General* section contains 9 items with a score range of 0 (best) to 6 (worst). The ratings received for each item in a section are summed and expressed as total score divided by the possible score. The possible score indicates the highest score obtainable by adding the maximum score for all items completed. An overall score for the whole scale is calculated by averaging the subscale scores for all the subscales rated for the patient. The rater of the PAS should obtain all necessary information from the patient interview as well as from available family members and from the patient's medical history. The PAS can be administered by a clinician with experience working with patients with schizophrenia after a short training. It takes approximately 45 minutes to complete the PAS.

The PAS will be administered in the local language. Only scales provided by Lundbeck designated provider, that have been validated in the language to which they have been translated will be used in this study.

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

9.1.2.2 Rater Qualification and Certification for PAS

The PAS should be administered by a clinician with experience working with patients with schizophrenia.

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. Exceptional situations must be discussed and approved by Lundbeck and/or designee.

Only raters who have been certified on a PAS study-specific rater training and certification programme will be authorized to rate the PAS for 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.

9.1.3 Diagnostic Assessments

9.1.3.1 Mini International Neuropsychiatric Interview for Psychotic Disorders Studies (MINI)

The MINI[38] is a structured diagnostic interview designed to provide a brief standardized evaluation of major Axis I psychiatric disorders in DSM-5™. In the study, the most current version of MINI 7 for DSM-5 will be used. 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 after a short training session.

It takes approximately 20 minutes to administer the MINI.

The MINI 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 will be provided to the site.

9.1.3.2 Rater Qualification and Certification for MINI

The MINI should be administered by clinicians (see 9.1.2.2) having experience in the diagnosis and treatment of patients with schizophrenia.

Only raters who have been certified on a MINI study specific rater training and certification programme will be authorized to rate the MINI for 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.

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 visits, 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.

9.1.5 Genotyping (Baseline 2)

Blood samples for CYP genotyping analysis will be collected in an EDTA tube (2x2 mL). The blood sampling and handling procedure are described in the study-specific *Laboratory Specification Manual* or equivalent.

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

- CYP2C19: *1 (WT), *2, *3, *4, *5, *6, *7, *8, *9, *10, and *17
- CYP2D6: *1 (WT), *2, *3, *4, *5, *6, *7, *8, *9, *10, *12, *14, *17, *29, *41 and *2×N (gene duplication)

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 enrolment in the study hence reported separately by the central/genotyping laboratory at study end.

The results will not be reported back to the investigator.

9.2 Efficacy Assessments

9.2.1 Use of Assessment Tools

The following assessment tools will be used:

- PANSS − clinician-rated, assessing symptoms of schizophrenia
- CGI-S − clinician-rated, assessing global impression
- NSA-16 – clinician-rated, assessing negative symptoms of schizophrenia
- BACS – clinician-administered, assessing cognitive function
- PSP – clinician-rated, assessing personal and social performance

The scales will be administered in local language or English. Only scales provided by Lundbeck designated provider, that have been validated in the language to which they have been translated will be used in this study.

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

9.2.1.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS[20] 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[39] (SCI–PANSS) will be used to facilitate the administration of the PANSS assessment.

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

9.2.1.2 Clinical Global Impression Scale – Severity (CGI-S)

The CGI[21,22] 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.

9.2.1.3 16-item Negative Symptom Assessment (NSA-16)

The NSA-16[23] is a clinician-rated scale designed to assess the presence, severity, and range of negative symptoms associated with schizophrenia. The NSA-16 consists of 16 items arranged in 5 subdomains: communication dysfunction (items 1 to 4), emotional/affective dysfunction (items 5 to 7), dysfunction in sociality (items 8 to 10), motivational/hedonic dysfunction (items 11 to 14), and reduced psychomotor activity (items 15 and 16), and a Global Negative Symptom Rating. NSA-16 items are rated on a 6-point scale from 1 (behaviour is normal) to 6 (behaviour severely reduced), and a score of 9 if the item is not-rateable. The Global Negative Symptom Rating is rated from 1 (no evidence of symptoms) to 7 (extremely severe symptoms). The 16 items are summed to yield a total score ranging from 16 to 96 and the global rating ranges from 1 to 7. The NSA-16 can be administered by an experienced clinician after a short training session.

It takes approximately 20 minutes to complete the NSA-16.

9.2.1.4 Brief Assessment of Cognition in Schizophrenia (BACS) – (US/Europe only)

The BACS[25, 26] is an assessment battery that assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome of patients with schizophrenia.

The BACS comprises six tasks for the evaluation of the following cognitive domains: Verbal Memory Test (verbal memory) score 0-75, Digit Sequencing Task (working memory) score 0-28, Token Motor Task (motor function) score 0-100, Verbal Fluency (semantic fluency and letter fluency) score 0-60, Symbol Coding Task (attention and processing speed) score 0-110, and Tower of London (executive functions) score 0-22. The score for each task is assessed by counting the number of correct answers. The BACS composite score is calculated by summing the z-scores for each of the six measures (obtained by comparing each measure with a normative sample of 400 controls matched to the 2005 Census) and dividing by the healthy control SD.[40] The BACS is designed for use by clinical psychologists, neuro-psychologists, or

clinicians with prior experience in administering cognitive tests in patients with schizophrenia.

It takes approximately 30 minutes to administer the BACS.

9.2.1.5 Personal and Social Performance Scale (PSP)

The PSP[24] 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.

9.2.1.6 Rater Qualification and Certification

The PANSS and NSA-16 should be administrated by clinicians (see 9.1.2.2) having experience in patients with schizophrenia and related psychotic disorders, and in administering the PANSS and NSA-16.

The CGI-S should be administered by the clinician (see 9.1.2.2) responsible for the patient.

The PSP should be administered by clinicians (see 9.1.2.2) having experience in patients with schizophrenia.

The BACS should be administered by a clinician (see 9.1.2.2) or clinical research assistant having experience in patients with schizophrenia and with cognitive testing.

Exceptional situations must be discussed and approved by Lundbeck and/or designee.

Only raters who have been certified on a PANSS, NSA-16, CGI-S, PSP and BACS study specific rater training and certification programme will be authorized to rate the scales for the study.

The PANSS and NSA-16 rater must be blinded to the protocol and to other patient data. Any exceptions must be discussed and approved by Lundbeck.

A CGI-S, PSP and BACS training session will be organized prior to the start of the study.

Each site should have a minimum of 4 raters in order to provide back-up for each other and allow switching between raters: two raters for the PANSS and NSA-16, blinded to the protocol and to the patient's treatment during the study, and two raters for the other scales,

who do not necessarily need to be blinded to the protocol and to the patient's treatment during the study.

Any exceptions must be discussed and approved by Lundbeck and/or designee.

The same blinded rater should not perform the PANSS and NSA-16 assessments at all the visits of a patient throughout the study. Instead, the two blinded raters should alternate performing these assessments at consecutive visits of a patient, or at a minimum, should alternate performing these assessments at the Baseline and at the Primary Outcome or Withdrawal Visits.

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. BACS raters will be trained by a third party vendor supervising the assessment of the BACS in this study. Lundbeck reserves the right to use external quality oversight methods (audio/video and worksheet review) to verify the accuracy of the PANSS scoring. The process for scale data oversight will be outlined in a separate document. Audio/video monitoring and review will be performed on behalf of Lundbeck by a third party vendor. The audios/videos will be uploaded to a server with limited and controlled access.

In specific regions, where appropriate, Lundbeck may choose to collect PANSS and NSA-16 scales' data by a centralized rating vendor who will assess patients in an independent interview conducted via real time videoconference.

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

9.3 Pharmacoeconomic Assessments

9.3.1 Use of Assessment Tools

The following assessment tools will be used:

- SWN-S − patient reported outcome, assessing subjective effects of neuroleptics
- DAI-10 – patient reported outcome, assessing attitude towards the use of antipsychotic medication

The scales will be administered in the local language. Only scales provided by Lundbeck designated provider, that have been validated in the language to which they have been translated will be used in this study.

The SWN-S and DAI-10 are patient-reported outcomes. Designated and trained site staff will be responsible for introducing and giving guidance to the patients on PRO completion. The training for the designed site staff will be provided by a third party vendor and should be completed before performing this task.

The patients' responses may only be corrected by the patient.

9.3.1.1 Subjective Well-Being under Neuroleptic Treatment – Short Version (SWN-S)

The SWN-S[27] 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.

9.3.1.2 Drug Attitude Inventory-10 (DAI-10)

The DAI-10[28] is a patient-rated scale designed to assess their attitude towards the use of antipsychotic medication and their experiences on these drugs. The DAI-10 consists of 10 statements, and the patient answers each statement as either true or false. Each answer is scored +1 or –1, and these are summed to give a total score ranging from +10 to –10: a negative total score indicates the patient has a "risk of non-compliance".

It takes 2 to 5 minutes to complete the DAI-10.

9.4 Pharmacokinetic Assessments

Blood samples (2 mL per time point) for Lu AF35700, Lu AF36152, olanzapine, risperidone, and 9-hydroxy-risperidone quantification in plasma will be drawn according to Panel 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual* or equivalent.

The plasma samples from Period B will be analysed for Lu AF35700 and the major metabolite Lu AF36152 using a bioanalytical method validated in accordance with the EMA *Guideline on Bioanalytical Method Validation*[41] and the FDA *Guidance for Industry*.[42]

The plasma samples from Period A and Period B will be analysed for olanzapine, risperidone, and 9-hydroxy-risperidone using a bioanalytical method validated in accordance with the EMA *Guideline on Bioanalytical Method Validation*[41] and the FDA *Guidance for Industry*.[42]

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.

If other metabolites are identified and considered significant, these may be included in an exploratory analysis.

9.5 Safety Assessments

9.5.1 Adverse Events

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

See chapter 10 for further information on adverse events.

9.5.2 Clinical Safety Laboratory Tests

The clinical safety laboratory tests are listed in Panel 3.

Panel 3 Clinical Safety Laboratory Tests

Haematology	**Liver**[a]	**Kidney**[a]
B-haemoglobin	S-total bilirubin (BILI)	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]	**Endocrine and Metabolic**[a]	U-Cocaine
S-cholesterol (total) (fasting)	S-albumin	U-Methadone
S-triglycerides (fasting)	S-glucose (fasting)	U-Opiates
S-low density lipoprotein (LDL)	S-prolactin [b]	U-Phencyclidine
S-high density lipoprotein (HDL)	B-HbA1c [c]	**Pregnancy (women only)**
	S-total protein	S-hCG 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 >250ng/mL (>5285mUI/L) will be reported by the central laboratory to the Medical Expert for clinical follow-up with the investigator.

c Performed at the Screening, Baseline 2 and Primary Outcome/Withdrawal Visits 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 2. The blood sampling and handling procedures are described in the study-specific *Laboratory Specification Manual* or equivalent.

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 stabilized or until the value has returned to a clinically acceptable value (regardless of relationship to the IMP). A patient with a value that is out-of-range at the Primary Outcome or Withdrawal Visit and considered clinically significant must be followed in accordance with usual clinical practice for up to 6 weeks or until the value normalizes or stabilizes 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 records.

Any out-of-range clinical safety laboratory test value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.5.3 Vital Signs

Pulse rate and blood pressure will be measured using a standard digital meter. Pulse rate and blood pressure will be measured in the following order: supine or sitting measurement after resting for 5 minutes followed by standing measurement after standing 1minute, and if required measured after 2 and/or 3 minutes to allow for evaluation of orthostatic hypotension.

Any out-of-range vital sign considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.5.4 Weight and Waist Circumference

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

Waist circumference should be recorded before the patient's meal and at approximately the same time at each visit. The measurement will be made by locating the upper hip bone and the top of the right iliac crest and placing a weighted measuring tape in a horizontal plane around the abdomen at the level of the crest. Before reading the tape measure, the assessor should ensure that the tape is snug, but does not compress the skin, and is parallel to the floor. The measurement is to be made at the end of a normal exhalation. Any weight change considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.5.5 Electrocardiograms (ECGs)

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

provided with the results and a cardiological interpretation of the ECG from the central ECG laboratory.

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

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

9.5.6 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.

Any abnormal finding or out-of-range value considered clinically significant by the investigator must be recorded as an adverse event on an *Adverse Event Form*.

9.5.7 Safety Assessment Tools

The following safety assessments will be administered:

- C-SSRS – clinician-rated assessing suicidality

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

Detailed instructions on how to administer the C-SSRS will be provided to the site.

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

The C-SSRS[43] is a semi-structured interview developed to systematically assess suicidal ideation and behaviour of patients participating in a clinical study. The C-SSRS has 4 questions addressing suicidal behaviour, 5 questions addressing suicidal ideation, and sub-questions assessing the severity.

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

An experienced clinician can use the C-SSRS after a short training session.

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

9.5.7.2 Rater Qualification and Certification

The C-SSRS should be rated by a clinician (see 9.1.2.2). Any exceptions must be discussed and approved by Lundbeck.

All raters must have, or obtain after training on the author's website, a valid C-SSRS Certificate of Training signed by the C-SSRS author Dr. Posner for archiving in the investigator TMF. No patient must be rated before the C-SSRS Certificate of Training has been delivered.

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

9.5.7.3 Order of Assessments

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

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

All visits other than the Screening Visit:
- PANSS
- NSA-16
- BACS
- SWN-S and DAI-10
- PSP
- C-SSRS
- CGI-S

9.6 Other Assessments

9.6.1 Blood Sampling for Pharmacogenetics – Optional

A blood sample (9 mL) will be collected in K3 EDTA tubes for subsequent DNA extraction at Visit 6. 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 but is not limited to single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). The analytical methods may be but is not limited to polymerase chain reaction (PCR), qPCR (quantitative PCR), sequencing,

or whole genome scans on microarrays. The details will be described in a separate protocol. The exploratory analysis results will not be a part of the Clinical Study Report but will be reported separately. The result of the exploratory analysis will not be reported back to the patient or the investigator.

9.6.2 Days of Hospitalization

If a patient is hospitalized due to schizophrenia during the study, this must be recorded in the e-CRF at each visit, including admission date and discharge date.

9.7 Biobanking

9.7.1 General Considerations

This study includes collection of blood samples for long term storage and use in a possible future explorative biomarker research study and collection of blood samples for separation of peripheral blood mononuclear cell (PBMC) to facilitate possible future generation of induced Pluripotent Stem Cells lines for studying disease aetiologies at the molecular and cellular level. PBMC isolation is restricted to sites within USA and may involve up to approximately 100 patients.

Although the possible future exploratory research studies will help to increase our understanding of the aetiology of schizophrenia and TRS and the molecular and cellular basis of the drug response, the efforts are strictly research based. Therefore, as the complex interactions between genes, biomarkers and disease biology are currently not characterized to a level that translates to a meaningful clinical advantage, individual results from the exploratory research studies will not be provided to neither the patient nor the investigator. For the same reasons, individual results will not be added to the patients' medical records.

The patients will have no direct benefit from the potential exploratory research studies.

As blood sampling for the exploratory genomics gene expression profiling, 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 and/or the establishment of cell lines from collected PBMCs is optional and a separate *Patient Information Sheet* covers these. Due to potential laboratory hazards associated with later handling of the PBMC based cell lines, all patients enrolled for PBMC collection must be tested for HIV, HBsAg, and anti-HCV.

The blood samples collected for the possible future exploratory biomarker analysis and the establishment of cell lines, or the data and cell lines 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.

The blood samples for genomics gene expression profiling, proteomics, and metabolomics analysis, and the cell line development 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[44] on pharmacogenetic terminology to ensure patient privacy protection.

Blood samples for biobanking will be collected as outlined in Panel 2.

9.7.2 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 25 mL. Samples for gene expression profiling will be shipped to a central laboratory, United States for sample storage.

9.7.3 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 50 mL. The samples for metabolomic/proteomic biomarkers will be shipped to a central laboratory, United States, for sample storage.

9.7.4 Blood Sampling for Pharmacogenetics

The optional 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, United States, 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.

9.7.5 Blood Sampling for Isolation of Peripheral Blood Mononuclear Cell (PBMC) (US only)

The optional blood samples for PBMC isolation will be collected in 4 x CPT Tubes (8 mL). The maximum volume of blood to be collected during the study for this purpose will be 32 mL. Blood tubes will be shipped on to a central laboratory where PBMCs will be isolated and retained. The PBMC aliquots will be shipped to a central laboratory, United States, for storage.

Later reprogramming of PBMC into pluripotent Stem Celle lines may enable generation of disease-affected cell types to be used for identifying novel therapies or for the identification of disease-specific phenotypes at the molecular, cellular and/or physiological level.

9.8 Total Volume of Blood Drawn and Destruction of Biological Material

The total volume of blood drawn from each patient will be approximately 250 mL (including the optional blood samples) 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 8.78.7) 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.

The isolated PBMC will be destroyed ≤20 years after the end of the study (see definition in section 8.7) by a central laboratory. The created stem cell lines may be kept indefinitely for research use.

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.

9.9 IMP Compliance

The responsible study personnel will dispense the IMP. Patients must be counselled on the importance of taking the IMP as directed at all study visits. The patient should bring the IMP (including emptied wallets) to site at each visit to verify compliance. Accountability and compliance verification should be documented in the patient's source documents and checked by the CRA during monitoring.

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

In addition Lundbeck reserves the right to use an external vendor for IMP adherence assessment. Details of such an IMP adherence application, if applicable, are described in the study specific guideline or equivalent.

10 Adverse Events

10.1 Definitions

10.1.1 Adverse Event Definitions[45]

Adverse event – is any untoward medical occurrence in a patient or 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 hospitalization or prolongation of existing hospitalization
- 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 hospitalization, but may jeopardize 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 hospitalization; or development of drug dependency or drug abuse.

Planned hospitalizations 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 adverse events. 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). In addition, 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.

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*[10] or the UK *Summary of Product Characteristics* for risperidone[35] and olanzapine,[36] 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 the patient's 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.

An uncomplicated pregnancy should not be reported as an SAE; hospitalization for a normal birth should not be reported as an SAE. If, however, the pregnancy is associated with an SAE, the appropriate serious criterion 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* (Partner Pregnancy ICF) 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 the IMP; action taken; and outcome. If the adverse event is not related to the IMP, an alternative aetiology must be recorded. 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).

If individual adverse events are later linked to a specific diagnosis, the diagnosis should be reported and linked to the previously reported adverse events.

10.4 Reporting Serious Adverse Events (SAEs)

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 *Serious Adverse Event Form* 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®(eCRF), then he or she must complete and sign the *Serious Adverse Event Fallback Form* and send it to:

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

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

It is the responsibility of the CRO to be aware of any local requirements, to inform the investigator of these, and to follow up on this.

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

Lundbeck will assume responsibility for reporting SUSARs to the authorities in accordance with local requirements. In those Member States of the European Union that have implemented the European Union *Clinical Trials Directive*[46] 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 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 IEC or IRB), 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, stabilized, 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 Visit must be handled in the same manner as SAEs that occur during the study. These SAEs will be recorded in the Lundbeck Safety database.

Patients with a clinically significant out-of-range clinical safety laboratory test value 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). If the clinically significant out-of-range clinical safety laboratory test value has not normalized or stabilized or a diagnosis or a reasonable explanation has not been established by the Safety Follow-up Visit, the investigator must decide whether further follow-up visits are required (this may include an additional medical examination and/or additional blood sampling). If further follow-up visits are made, these must be documented in the patient's medical records and not in the eCRF.

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

11 Data Handling and Record Keeping

11.1 Data Collection

11.1.1 Electronic Case Report Forms (eCRFs)

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

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

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

11.1.2 Patient Binders

11.1.2.1 Use of Patient Binders

Lundbeck or designee will provide a *Patient Binder* for each patient. The *Patient Binder* contains different types of source documents, organized 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 following electronic data will be transferred by the vendors and kept in a secure designated storage area outside the eCRF:

- The clinical safety laboratory test results including infectious status testing will be transferred to Lundbeck Department of Biometrics by central laboratory.
- The in study pharmacogenetics (Baseline 2) data will be transferred to Lundbeck Department of Biometrics by central laboratory.

- Lu AF35700, Lu AF36152, risperidone (including 9-hydroxy-risperidone) and olanzapine PK supportive data will be transferred to Lundbeck Department of Biometric and Lundbeck Department of Bioanalysis by central laboratory.
- Biobank supportive data for gene expression profiling (RNA), Metabolomics/proteomics (plasma) and pharmacogenetic and PBMC will be transferred to Lundbeck Department of Biometrics by central laboratory.
- For electronic assessment tools (for example PANSS, CGI-S, PSP, and NSA-16), the data will be transferred to Lundbeck Department of Biometrics by the designated vendor.
- The ECG results will be transferred to Lundbeck Department of Biometrics by central ECG service provider.

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 until the study has been completed. After the study has been completed, all user access to the eCRF will be revoked. Renewed access to the eCRF will be given if corrections or updates to the database are required.

At the end of the study, the site will be provided with all data related to the site (including eCRF data, queries, and the audit trail) using a secure electronic medium; the secure storage of these data at the site is the responsibility of the investigator. When confirmation of receipt of the data has been received from all sites, all user access to the eCRF will be revoked. If, for some reason, the data are not readable for the full retention period (25 years or in accordance with national requirements, whichever is longer), the investigator may request that the data related to the site be re-sent.

11.2.2 Other Study Documents

The investigator must keep the investigator's set of documents in the investigator TMF for at least 25 years after the *Clinical Study Report* has been approved or in accordance with national requirements, whichever is longer.

Lundbeck or designee will remind the investigator in writing of this obligation when the *Clinical Study Report Synopsis* is distributed to the site.

12 Monitoring Procedures

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

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*.[15] In addition, the CRA will be available for discussions by telephone.

In addition, the CRA will visit the site and review the screening log (or equivalent) maintained by the site which indicates the number of patients with ED and LD TRS who have entered the study. The CRA will advise the site regarding adjustments to further enrolment that may need to be made at their site to satisfy the appropriate ratio of patients with ED TRS to patients with LD TRS that may enter the study based upon updates of global enrolment patterns.

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

Any assessment tool ratings (rating scales) recorded directly on the electronic device will be considered source data.

It must be possible to verify all other data in the eCRFs against source documents in the patients' medical record, or in the location stated in the source data agreement.

13 Audits and Inspections

Authorized personnel from Clinical Quality Assurance, H Lundbeck A/S, 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*[15] and all other relevant regulations.

The patients must be informed that authorized 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 request relevant parts of medical records. No personal identification apart from the screening or randomization number will appear on these copies.

Patient data will not be disclosed to unauthorized third parties, and patient confidentiality will be respected 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 evaluation changes after the study is terminated, 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, secondary and exploratory objectives)

- Change from Baseline 2 to Week 14 in PANSS total score

16.2 Key Secondary Endpoints

Clinical impression (supportive of primary and secondary objectives)

- Change from Baseline 2 to Week 14 in CGI-S score

Functioning (supportive of explorative objective)
- Change from Baseline 2 to Week 14 in PSP total score

16.3 Secondary Endpoints

Global clinical impression (supportive of primary and secondary objectives)
- Change from Baseline 2 to Week 14 in CGI-S score

Proportion of responders at Week 14 (supportive of primary and secondary objectives)
- Responders criteria will be blinded to investigator and described in the *Clinical Study Protocol Addendum - Unmasked Information*.

Negative symptoms (supportive of secondary objective)
- Change from Baseline 2 to Week 14 in NSA-16 total score
- Change from Baseline 2 to Week 14 in PANSS Negative Factor Score (Marder Negative Score)

16.4 Exploratory Endpoints

Cognitive performance (supportive of explorative objective)
- Change from Baseline 2 to Week 14 in BACS score

Functioning (supportive of exploratory objective)
- Change from Baseline 2 to Week 14 in PSP total score

Analysis of patient historical and demographic predictors of response (supportive of exploratory objective) in:
- Patients with ED TRS
- Patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit
- Patients with ED TRS *versus* LD TRS
- Patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit *versus* patients with LD TRS
- Genetic analysis (for example CYP genotyping and polygenetic risk-score)

16.5 Safety Endpoints
- Adverse events
- Absolute values and changes from Baseline 2 in Phase B 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

17 Statistical Methodology

17.1 Responsibilities

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

The population (pop) PK analysis will be performed and reported separately by the *Department of Quantitative Pharmacology*, H. Lundbeck A/S, or a designee CRO.

17.2 Analysis Sets

The following analysis sets will be used to analyse and present the data for each of the above groups of patients:

- all-patients-treated set Period A (APTS_A) – all patients who took at least one dose of IMP during Period A (risperidone or olanzapine)
- all-patients-treated set (APTS) – all randomized patients who took at least one dose of double-blind IMP (Lu AF35700, risperidone, or olanzapine) after randomization (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.

17.4 Patient Disposition

Patient disposition will be summarized by treatment group and include the number of patients who completed 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 summarized for the APTS_A by risperidone/olanzapine treatment group and for the APTS by randomized treatment group.

The number of patients who withdrew from treatment will be summarized 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 summarized for the APTS_A by risperidone/olanzapine treatment group. Withdrawals during Period B will be summarized for the APTS by randomized treatment group.

Separate summaries of reasons for withdrawal from treatment will be presented by randomized treatment group for withdrawn patients who returned to the Efficacy Follow-up Visit.

17.5 Demographics and Baseline Characteristics

Demographics (sex, age, race), other baseline characteristics (for example height, weight, BMI, and mean waist circumference, number of years from first schizophrenia diagnosis, and number of failed antipsychotic treatment episodes), and baseline efficacy variables will be summarized by treatment group.

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

17.6 Recent and Concomitant Medication

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

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

17.7 Exposure and Compliance

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

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

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

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

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

17.8 Period A Evaluation

The percentage of patients responding to treatment at Weeks 1, 2, 4, and 6 as well as at any of those weeks will be summarized by treatment (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 summarized by week number for the total patients in APTS_A and by treatment (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 two-sided significance level of 0.05 is used unless otherwise indicated. For all endpoints, the effects of Lu AF35700 will be evaluated by testing the null hypothesis of no difference to the risperidone/olanzapine group.

17.9.2 Analysis of the Primary Endpoint

Changes from Baseline 2 in total PANSS score at Weeks 7, 8, 10, 12, and 14 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 14 from withdrawals will not be included in the primary analysis.

The model will include the fixed, categorical effects of treatment (Lu AF35700 and risperidone/olanzapine groups), strata (ED and LD), country, visit, treatment-by-visit interaction, strata-by-visit interaction, fixed covariates of baseline scores (Baseline 1 and Baseline 2) and baseline scores-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If this analysis fails to converge, the following within patient (co)variance structures will be applied, in the listed 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 difference between Lu AF35700 and risperidone/olanzapine at Week 14 based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between Lu AF35700 and risperidone/olanzapine based on this model will be reported with two-sided symmetric 95% confidence intervals and corresponding p-values.

In addition to the analysis specified above, the following analysis will be performed for the primary endpoint, supportive of secondary and exploratory objectives:

The changes from Baseline 2 to Week 14 in PANSS total score for patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit, ED TRS, LD TRS, ED TRS versus LD TRS, and patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit versus LD TRS will be examined using the same methodology as described for the primary endpoint. The model will include the fixed, categorical effects of treatment (Lu AF35700 and risperidone/olanzapine), subgroup, country, visit, treatment-by-visit-by-subgroup interaction, and fixed covariates of baseline scores (Baseline 1 and Baseline 2) and baseline scores-by-visit interaction. The patients will be classified into subgroups according to whether they were first diagnosed with schizophrenia ≤5 years prior to the Screening Visit, between 5 and 10 years prior to the Screening Visit, or ≥10 years prior to the Screening Visit. From this model, the difference between treatments within each subgroup at Week 14 will be derived from the treatment-by-visit-by-subgroup interaction. Also, this interaction will be used to explore the efficacy in patients with ED TRS versus LD TRS by estimating (AF35700 ED – risperidone/olanzapine ED) versus (AF35700 LD – risperidone/olanzapine LD). In the same way, the efficacy in patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit versus patients with LD TRS will be explored.

17.9.3 Sensitivity Analyses of the Primary Endpoint

Some level of missing data is expected, and the primary analysis, MMRM, is valid under the assumption that the data is Missing at Random. Simulation studies do suggest that MMRM is sufficiently robust to accommodate some level of data Missing Not at Random (MNAR). Since it is unclear to which degree missing data will be of the MNAR type, 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.[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).

The primary analysis will be repeated for the subgroup of patients that were randomized after protocol amendment PA3 was approved in the relevant country.

17.9.4 Testing Strategy for Primary and Key Secondary Endpoints

If Lu AF35700 is superior to risperidone/olanzapine for the primary endpoint, the null hypothesis of no difference between Lu AF35700 compared to risperidone/olanzapine will be tested for the key secondary endpoints in the following order:

1. Change from Baseline 2 to Week 14 in CGI-S score
2. Change from Baseline 2 to Week 14 in PSP total score

Change in PSP will only be tested if Lu AF35700 is superior to risperidone/olanzapine for CGI-S.

No multiplicity corrections will be applied for secondary and exploratory endpoints.

17.9.5 Analysis of the Key Secondary and Secondary Endpoints

For the analysis of the CGI-S, PSP total score, NSA-16, and PANSS Negative Factor scores, the same model as that described for the primary endpoint will be used.

The proportion of patients responding at Week 14 will be compared for Lu AF35700 *versus* risperidone/olanzapine using logistic regression with strata, country and treatment as factors and baseline PANSS total scores (Baseline 1 and Baseline 2) as covariates. The analysis will be done for observed cases without imputation, as well as for the whole FAS, imputing non-response for all patients discontinued prior to Week 14. The definition of response will be defined in the statistical analysis plan.

Additional responder analyses using alternative cut-offs of the primary endpoint will 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 the analysis of BACS and PSP, the same model as that described for the primary endpoint will be used.

The proportion of patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit, patients with ED TRS, LD TRS, the difference between the proportions of patients with ED TRS and LD TRS, and the difference between the proportions of patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit and LD TRS responding at Week 14 will be compared for Lu AF35700 *versus* risperidone/olanzapine using logistic regression with country as a factor and treatment-by-subgroup interaction and baseline (Baseline 1 and Baseline 2) PANSS total score as covariate. The analysis will be done for observed cases without imputation, as well as for the whole FAS, imputing non-response for all patients discontinued prior to Week 14. Similar to the secondary endpoint, different response criteria will be investigated.

The analyses described above assess the distinct categorical effect of early-in-disease and late-in-disease. Furthermore, the effect of number of years from first schizophrenia diagnosis,

and number of failed antipsychotic treatment episodes will be investigated by performing MMRM and logistic regression models with the different predictors included as factors or covariates, both interacting with treatment, as appropriate. These analyses will be detailed in the statistical analysis plan.

The effect of genetic analysis will be investigated for the primary and secondary endpoints. These analyses will be detailed in a separate protocol (and statistical analysis plan), and reported separately.

The effect of MMN at Baseline 2 will be investigated for the primary and secondary endpoints by including the amplitude of deviant response to auditory stimulus as covariate in MMRM and logistic regression models similar to those described above. In addition the change in MMN from Baseline 2 to Week 14 will be summarised. These analyses will be detailed in the statistical analysis plan.

17.9.7 Analysis of Subgroups

Per design of the study, there are two distinct subgroups: patients with ED TRS and those with LD TRS. In addition, there is a subgroup of the ED TRS population defined as patients with TRS first diagnosed with schizophrenia ≤5 years prior to the Screening Visit. The analyses for these are described above.

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 14). Two analyses will be performed:

1. Include patients with values > LLOQ at Weeks 8, 10, and 14
2. Selection of patients based on population pharmacokinetic analysis. This analysis will be reported separately

17.9.8 Pharmacokinetic Analysis

The population pharmacokinetics of Lu AF35700, olanzapine and risperidone/ 9-hydroxy-risperidone will be assessed by means of nonlinear mixed effect modelling, including covariate analysis. If deemed relevant, exploratory pharmacokinetic/pharmacodynamic (PK/PD) analysis will be performed, which will be specified in the population PK/PD analysis plan, prepared by the Department of Quantitative Pharmacology, Lundbeck, before the study is unblinded. The results from the analyses will be reported by the Department of Quantitative Pharmacology, or designee CRO, in a separate population PK/PD report.

Individual oral clearance estimates will be estimated for each drug (Lu AF35700/olanzapine/risperidone) and be compared with historical data in order to find extreme values. The extreme clearance values will together with plasma concentrations below LLOQ form the basis for identifying patients with extremely low plasma concentrations to be used for the analysis of subgroups (see section 17.9.7). Further details will be given in the population PK/PD analysis plan.

Plasma concentrations of Lu AF35700 and metabolite (Lu AF36152), risperidone, 9-hydroxy-risperidone, and olanzapine, as well as CYP genotype will be listed.

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 summarized by randomized treatment group for the APTS and by treatment for APTS_A.

Information from the optional exit interview related to AEs (serious and non-serious) shall flow back to the investigator via a special AE report prepared for exit interviews. The non-serious AEs reported during these interviews will be reported in separate listings in the CSR. The serious AEs shall be reported as specified in this protocol for SAEs occurring in the safety follow up period.

Allocation of TEAEs to Study Periods

TEAEs will as a minimum be allocated into study Periods A and B. Further division may be performed. This 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 summarized by randomized treatment group using descriptive statistics. Potentially clinically significant (PCS) values will be flagged and summarized.

All safety analyses for period B will be based on the APTS, and all safety analyses for period A will be based on APTS_A.

17.11 Interim Analyses

No interim analyses are planned.

17.12 Sample Size and Power

The study will include 245 randomized patients per group in Period B.

Assuming a common standard deviation of 15, there is approximately 93% power for showing a mean improvement in change in PANSS total score of 5.25 (standardized effect size 0.35) of Lu AF35700 over risperidone/olanzapine with 196 patients per treatment arm.

Assuming an information loss of ~20% due to dropout in Period B, n=245 (=196/0.8) will be randomized to each treatment group, bringing the total number of randomized patients to 490.

With an attrition rate of ~40% in Period A, approximately 817 (=490/0.6) patients are expected to be enrolled to meet the target of randomizing 490 patients in Period B.

A blinded re-assessment of sample size will be considered if the blinded standard deviation estimate or the dropout rate deviates from the assumptions. A maximum of 300 randomized 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, that is:

The model will include the fixed, categorical effects of country, visit, stratum-by-visit interaction as well as the fixed covariates of baseline scores (Baseline 1 and Baseline 2) and baseline scores-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient errors.

17.13 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 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 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.

Lundbeck will submit results information
- to ClinicalTrials.gov
- to EudraCT

The primary publication based on this study must be published before any secondary publications.Authors of the primary publication must fulfil the criteria defined by the *International Committee of Medical Journal Editors* (ICMJE).[48]

18.4 Summary of Clinical Study Results

Upon completion of the study and when the study results are available, the patient has the right to be informed by the investigator about the overall study results.

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*.[15]

20 Finance

20.1 Site Agreements

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

20.3 Equipment

Equipment owned or rented by Lundbeck that has been provided to the sites 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 Authorization

Clinical Study Protocol
Authentication and Authorization

Study title:	Interventional, randomized, double-blind, active-controlled study of the efficacy of Lu AF35700 in patients with early-in-disease or late-in-disease treatment resistant schizophrenia
Study No.:	17303A (Anew)
Edition No.:	4.0
Date of edition:	7 September 2018

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 Medical Safety	[redacted]

Authorization

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

Head of Clinical Research Development Psychiatry:	[redacted]

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

Recent and Concomitant Medication: Disallowed or Allowed with Restrictions

Drug Class	Details
Any investigational drug	– Prohibited <30 days before the Screening Visit
Antidepressants	– Patients must not initiate any antidepressants in this study. Patients who have been treated with the same antidepressant for at least 3 months prior to Visit 1 may continue on this antidepressant in the study as long as its continuation on stable dose is anticipated throughout the study.
Anticonvulsants	– Prohibited <7 days before Baseline 1
Antipsychotics	– Except for risperidone or olanzapine supplied as IMP – 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 should be avoided. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the anticholinergic medication documented, including a notation of the drug name, dose, and time of administration on the eCRF.
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, 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 should be avoided. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of the anxiolytics or hypnotics documented, including a notation of the drug name, dose, and time of administration on the eCRF.
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; 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 (oral, patch), 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 60mg/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 should be avoided. However, if delaying administration of efficacy and safety scales is not feasible, the scales should still be administered and the use of propranolol documented, including a notation of the drug name, dose, and time of administration on the eCRF.
[Country-specific Protocol Amendment 1 for UK: Concomitant drugs associated with risk of QT prolongation	- *As all the IMPs have a risk of QT prolongation, clinicians should use caution when prescribing the concomitant use of drugs associated with a risk of QT prolongation in this study, especially in the elderly.]*

Prohibited CYP Sub-enzyme Influencing Medications

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

a Short term use for allergy is permitted