Statistical Analysis Plan

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
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List of Abbreviations and Definitions of Terms

ADaM	Analysis Data Model
AE	Adverse event
ALT	alanine aminotransferase
APES	all-patients-enrolled set
APRS	all-patients-randomized set
APTS	all-patients-treated set
APTS_PC	all-patients-treated set prospective confirmation period
BACS	Brief Assessment of Cognition in Schizophrenia
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CSR	Clinical Study Report
DILI	potential drug-induced liver injury
eCRF	electronic case report form
ED	Early-in-disease
FAS	full-analysis set
IMP	investigational medicinal product
LD	Late-in-disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PCS	potentially clinically significant
PSP	Personal And Social Performance
PYE	patient years of exposure
QQ	quantile-quantile
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	statistical software package from the SAS® Institute
SDTM	Study Data Tabulation Model
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFL	Tables, Figures and Listings
TRS	Treatment resistant schizophrenia
WHO-DDE	World Health Organization Drug Dictionary

Consequences of Early Study Termination

After the results from the first pivotal study with Lu AF35700 in treatment-resistant schizophrenia patients, Study 16159A, were revealed, it was decided to prematurely terminate Study 17303A. At the time of study termination, a total of 68 patients were randomized, compared to the 150 patients originally planned (plus approximately 20 patients from Japan). As a consequence some of the planned analyses will no longer be performed, due to the low number of patients randomized. In particular, no subgroup analyses will be performed, including the analyses for early-in-disease and late-in-disease patient populations and analyses of age sex, race, regional or baseline characteristics. The detailed changes can be seen in Section 18. For traceability, the original objectives are kept, but the endpoints and statistical analyses presented in the SAP will reflect the set of analyses that will be done.

1 Objectives

1.1 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)

For definitions of ED and LD, see section 3.1.

1.2 Secondary Objective

- 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

1.3 Exploratory Objective(s)

- 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

1.4 Safety Objective(s)

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

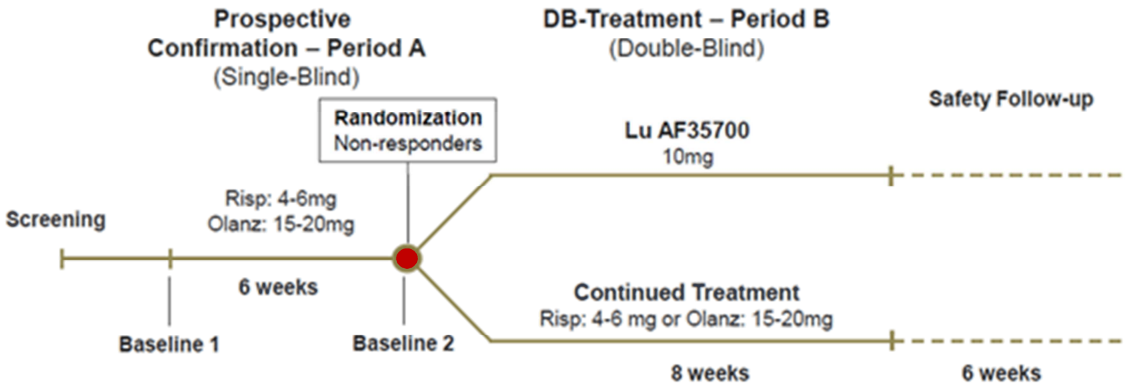
2 Study Design

This is an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, active-controlled, fixed-dose study. The time point of randomization was blinded to patients and blinded rater.

An overview of the study is presented in Panel 1. The criteria for response/non-response evaluated at Baseline 2 were kept blinded to patients and investigators.

Patients were randomized in Period B (randomization ration 1:1 to Lu AF35700 10 mg, or continued risperidone/olanzapine). Within the ED and LD subgroups, patients were stratified, ensuring an equal proportion of patients randomized to each treatment.

Panel 1 Study Design



NOTE: Randomized patients will be stratified in both Period B treatment arms across early-in-disease and late-in-disease patients (approx 2:1)

The study includes an efficacy follow-up of withdrawn patients at the projected time of the primary endpoint. 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.

3 Definitions

3.1 Definition of Early-in and Late-in-Disease

Early-in-disease (ED): 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).

Late-in-disease (LD): 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)

3.2 Definition of Baseline

There are two baselines defined in this study (for details about data handling, see section 19.2):

Baseline 1 - the latest value captured at or before nominal Visit 2 (Week 0 of Period A).

Baseline 2 (randomized patients) – for efficacy variables the latest value captured at or before nominal Visit 6 (Week 0 of Period B), and for pharmaco-economic and safety variables the latest value captured at nominal Visit 6

For C-SSRS, the Baseline 1 will be the assessment at Visit 2, and no Baseline 2 will be defined (see section 13.6.1).

In the TFLs and CSR, Baseline 1 will be named Baseline and Baseline 2 will be named Randomization.

3.3 Definition of Periods

Classification of adverse events into periods is defined in section 13.1.4.

For other data, assessments from the withdrawal visit and unscheduled visits will be assigned to a nominal visit (see section 19.2.1 and 19.2.2), and then all nominal visits will be assigned to a period:

- *Screening Period* (3 weeks) - Starts at the Screening Visit and continues up to, and including, Visit 2
- *Period A* (6 weeks) - Starts after Visit 2 and continues up to, and including, Visit 6
- *Period B* (8 weeks) - Starts after Visit 6 and continues up to, and including, Visit 11
- *Follow-Up Period* - Starts after last Visit in Period A (non-randomized patients) or B (randomized patients)

In the TFLs and CSR, Period A will be named Prospective Confirmation Period, and Period B will be named Double-blind Treatment Period.

4 Endpoints

Data handling rules are described in the sections 19.1 and 19.2.2.

In the TFLs and CSR, Baseline 2 in the endpoints will be named Randomization, and week will be specified relative to Period B, e.g. the primary endpoint will be *Change from Randomization to Week 8 in PANSS total score*.

4.1 Primary Endpoint

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

4.2 Secondary Endpoints

- Change from Baseline 2 to Week 14 in CGI-S score
- Proportion of responders at Week 14 (supportive of primary and secondary objectives) (Response defined as ≥ 20% reduction in PANSS total score from Baseline 2)

- 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)

4.3 Exploratory Endpoints

- Change from Baseline 2 to Week 14 in BACS score
- Change from Baseline 2 to Week 14 in PSP total score

4.4 Safety Endpoints

- Adverse events
- Absolute values and changes from Baseline 2 in Period 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

5 Analysis Sets

The sets of patients to be analysed are defined as follows:

- *all-patients-enrolled set* (APES)
- *all-patients-treated set prospective confirmation period* (APTS_PC) – all patients who took at least one dose of study medication during Period A (risperidone or olanzapine)
- *all-patients-randomized set* (APRS) – all patients randomized
- *all-patients-treated set* (APTS) – all randomized patients who took at least one dose of double-blind study medication (Lu AF35700, risperidone, or olanzapine)
- *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. Assessments made at the Efficacy Follow-up Visit will not be considered as valid post-baseline assessments for classification into FAS

The patients and data will be classified into the analysis sets during a Classification Meeting according to the definitions above after the study database has been released, but before the blind has been broken.

Note, in the protocol, APTS_PC was named all-patients-treated set Period A (APTS_A).

6 Descriptive Statistics

Unless otherwise specified, summary statistics (n, arithmetic mean, standard deviation [SD], 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.

Unless otherwise specified, data listings will include site, period, treatment group (for randomized patients both treatment group in Period A and randomized treatment group will be included), patient screening number, sex, age, race, and weight at Baseline (for randomized patients weight at both Baseline 1 and Baseline 2 will be included).

Summaries for Period A will be based on APES or APTS_PC, and will be done by Period A treatment group (risperidone and olanzapine) for safety, and for the total group for efficacy. Summaries for Period B will be based on APRS or APTS, and will be done by randomized treatment group (LuAF35700 and risperidone/olanzapine).

7 Patient Disposition

7.1 Summary of Patient Disposition

Patient disposition for Period A will be summarized for the APES, and for Period B for the APRS.

Patient disposition will include the number of patients who completed treatment, and the number of patients who withdrew from treatment, as well as the number of patients in each analysis set defined for the period (see section 5). The summaries for Period A will also include number of screened patients and number of screening failures.

7.2 Withdrawal

Withdrawal summaries and plots will be presented separately for Period A and B and based on APTS_PC and APTS, respectively.

Withdrawals from treatment in Period A and Period B will be summarized by primary reason for withdrawal as well as by all reasons for withdrawal based on the APTS_PC and APTS, respectively.

Summary of patients who were withdrawn from treatment in Period A due to efficacy response or not being adherent (taking less than 80% of assigned IMP during Period A) are described in section 11.

Patients who withdrew from treatment or study will be listed. The listing will include both periods, indicating the period when the patient was withdrawn, the reason type (primary and secondary reason for withdrawal from treatment), the reason, specification of other reason, the number of days from Visit 2 until withdrawal from treatment, the number of days on IMP (IMP in Period A for non-randomized patients and IMP in Period A – IMP in Period B for randomized patients), and a flag indicating if drug code was broken.

Kaplan-Meier plots of time to withdrawal from treatment in Period B will be presented based on the APTS. The time will be calculated from the date of first dose of IMP in Period B to the

date of completion or withdrawal from treatment. Patients who completed treatment will be regarded as censored.

8 Demographics and Other Baseline Characteristics

The summaries will be done for APTS_PC and APTS.

Demographics (sex, age, and race), height, weight, BMI, and waist circumference at Baseline 1, years since diagnosis of schizophrenia (both as continuous and in categories ≤ 5 years, 6-9 years and ≥ 10 years), Premorbid Adjustment Scale (PAS), social histories, and efficacy variables at Baseline 1 will be summarized. For patients in the APTS, weight, BMI, waist circumference, and efficacy variables at Baseline 2 will also be summarized.

From the lifetime schizophrenia history collected, the following parameters will be summarised:

- Duration of untreated psychosis: Time from first psychotic symptoms to date of first antipsychotic drug treatment or first psychiatric hospitalization for psychosis
- Number of antipsychotic treatment periods and response
    - Treatment periods: Antipsychotic treatment answered yes
    - Adequate treatment periods: Antipsychotic treatment, adequate duration, adequate dose and considered predominantly adherent all answered yes
    - Adequate periods with adequate response: Adequate treatment period and demonstrate adequate response answered yes
    - Adequate periods without adequate response: Adequate treatment period and demonstrate adequate response answered no
- Cumulative time in symptomatic psychosis: Cumulative time of all periods where persistent psychotic symptoms answered yes (regardless whether any treatment was administered or treatment period was adequate or not)
- Demonstration of tolerance: Treatment periods where tolerance to antipsychotic drug treatment is answered yes
- Tardive dyskinesia: Treatment periods where persistent tardive dyskinesia is answered yes
- Hospitalizations: Periods with a new hospitalization
- Clozapine treatment trials: Number of adequate treatment periods where patient received treatment with Clozapine

Details for handling (partially) missing dates is described in Section 19.3.2.

Concurrent as well as relevant past medical, and neurological, and psychiatric disorders will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized.

A concurrent medical, neurological or psychiatric disorder is a disorder that is ongoing at the Screening Visit. A past medical, neurological or psychiatric disorder is a disorder that ended prior to the Screening Visit.

9 Recent and Concomitant Medications

Recent and concomitant medication will be coded using the WHO Drug Dictionary (WHO-DDE).

Medications will be classified into categories according to the start and end date. Handling of missing or incomplete dates are specified in section 19.3.4.

The following categories will be defined:

- Medications started before first dose of IMP in Period B and discontinued prior to first dose of IMP in Period B (randomized patients in APTS) or started before Follow-up Period (non-randomized patients and randomized patients not in APTS)
- Medication started before first dose of IMP in Period B and continued after first dose of IMP in Period B
- Medication started at or after first dose of IMP in Period B and at or before Visit 11 (Primary Outcome or Withdrawal Visit)
- Medication started after Withdrawal Visit for Patients Withdrawn from Treatment in Period B and before the efficacy follow-up Visit

Medications will be summarized by anatomical therapeutic chemical (ATC) code levels 2 and 3, and generic drug name. The three first categories will be summarized separately.

All disallowed medications will be listed based on the APES. The listing will include the generic drug name, the duration, the start and end dates, and dosing information.

10 Exposure and Compliance

Exposure (days) to IMP will be defined for Periods A and B as:

Last date of IMP in the Period - Start date of IMP in the Period + 1.

Compliance for Periods A and B is defined as the percentage of planned medication taken by patients while enrolled in the study.

Compliance (%) with IMP for a period will be defined as:

$$\frac{\text{End date period} - \text{ Start date period} + 1 \ - \text{Number of non-compliant days}}{\text{End date period} - \text{Date of first IMP in period} + 1} \times 100$$

End date period for Period A is Visit 6/Withdrawal visit (patient withdrawn from treatment in Period A) and for Period B Visit 11/Withdrawal Visit. *Number non-compliant days* is defined as the sum of all non-compliant days reported in the period. A *Non-compliant day* is defined as a day on which no IMP has been taken, less than the full dose of IMP has been taken, or more than the full dose of IMP has been taken.

Compliance will also be calculated separately for missed/less than full dose (using *Number of days with missed or less than full dose* in the compliance formula), and overdoses (using *Number of days with overdoses* in the compliance formula).

Exposure, including patient years of exposure (PYE) and compliance, and mean plasma concentration at Week 2 and 4 in Period A will be summarized for patients in APTS_PC (see Section 11). PYE will be calculated as the sum of the number of days of exposure to IMP for each patient in a period, divided by 365.25 days.

The final dose level of risperidone/olanzapine that patients were titrated to in Period A will be summarized by risperidone/olanzapine therapy group for the ATPS_A and ATPS.

Exposure and compliance in Period B will be summarized for the APTS.

Compliance with IMP will be categorized as ≤80% or >80% within each period. The number and percentage of patients in each category for Period A will be summarized based on the APTS_PC, and for Period B based on the APTS. The summary based on APTS_PC will also be done by Period A non-response or response.

11 Period A Evaluation

The PANSS total score; PANSS Negative Symptoms, PANSS Positive Symptoms, and PANSS General Psychopathology subscale scores, and CGI-S score at Baseline 1 and in Period A will be summarized by week based on the FAS.

The time in the TFLs and CSR will be the nominal week in Period A, i.e. 0, 1, 2, 4, and 6.

12 Efficacy

12.1 General Efficacy Analysis Methodology

For details about data handling, see section 19.1 and 19.2.2.

If not otherwise stated, the efficacy analyses will be based on the FAS. For all endpoints, the effects of Lu AF35700 will be evaluated by testing the null hypothesis of no difference to the active control (risperidone or olanzapine).

The efficacy data collected after withdrawal from treatment were collected for a specific type of sensitivity analyses, which will no longer be performed. So the efficacy follow-up data collected will not be included in any efficacy analyses.

All tables and graphs will be presented by randomized treatment group.

All the p-values will be based on two-sided tests; the confidence intervals (CIs) will be two-sided, and all analysed endpoints will be presented with p-values and 95% CIs.

If not otherwise specified, the time in the TFLs and CSR will be the nominal week in Period B, i.e. 0, 1, 2, 4, 6, and 8. In the following description of the endpoints and analyses related to Period B, the time from Baseline 2 will be used.

Descriptive statistics for the absolute-and change from Baseline 2 efficacy scores will be presented by week in Period B. The summaries for the absolute scores will also include the Baseline 2 value.

12.2 Testing Strategy

No multiplicity corrections will be applied.

12.3 Analysis Methodology for the Primary Endpoint

12.3.1 Primary Analysis of the Primary Endpoint

Changes from Baseline 2 in PANSS total score at Weeks 1, 2, 4, 6, and 8 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.

The model will include the fixed, categorical effects of treatment (Lu AF35700 and risperidone/olanzapine groups), strata (ED and LD), visit, treatment-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 SAS code for the primary analysis is shown in Appendix III.

The primary comparisons will be the difference between Lu AF35700 and risperidone/olanzapine at Week 8 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.

12.3.2 Rationale for Selected Analysis Method for the Primary Endpoint

The collected assessments from the PANSS total score are generally considered as continuous endpoints, and they are analysed using methods based on observations following a normal distribution. Given the repeated observation of approximately normally distributed data, an MMRM analysis using all available data is chosen for the primary analysis. Covariates are included in the model based on an approach including key factors representing study design features (visit, treatment and stratification factor (ED, LED)), and baseline and randomization levels of PANSS total score to account for differences in baseline and randomization level of

the PANSS total score and its predictive ability. When the MMRM analysis includes the individual factors mentioned as well as interaction of visit and treatment, and visit and baseline/randomization scores, and applies an unstructured covariance, as described in section 12.3.1, it allows for flexibility in modelling the development over time and similarly provides robust estimation, even under some deviation from the assumption of normality.

This MMRM analysis estimates the treatment difference that would have been seen, had the drug been taken as directed. The pharmacological effect estimated by this MMRM analysis is considered a relevant measure to evaluate the efficacy of treatment in schizophrenia. In schizophrenia symptoms are treated, and therefore it is considered clinically relevant to investigate the effect that can be obtained on symptom level, if the prescribed medication treatment is taken in the prescribed period.

The MMRM analysis provides an unbiased estimate of the treatment effect under the assumption that missing data are missing-at-random (MAR). Published data support the robustness of the MMRM analysis regarding protection against type I error and against bias, also in situations with a non-negligible proportion of missing data. Using extensive simulations, it has been demonstrated that the type I error is only affected to a limited extent and that the bias is small under the assumption that 1/3 of the missing data are missing-not-at-random (MNAR), even when there is a severe imbalance between the treatment groups in the proportion of withdrawals.[1]

12.3.3 Evaluation of Model Assumptions for the Primary Analysis of the Primary Endpoint

The assumption of normality will be investigated on an exploratory basis by inspection of a QQ-plot of the residuals.

The assumption of homoscedastic residuals will be investigated on an exploratory basis by inspection of a scatter-plot of the residuals versus the fitted values and by week.

12.4 Analysis of the Secondary Endpoints

Change from Baseline 2 in CGI-S, NSA-16 and PANSS Negative Factor Score (Marder Negative Score) will be analyzed using the same methodology as that described for the primary endpoint (see section 12.3.1).

Response is defined as ≥ 20% reduction in PANSS total score from Baseline 2. Please note, that for calculation of percentage change in PANSS total score, 1 will be subtracted from each item before calculating the percentage change, see section 19.1.

The proportion of patients responding at Week 8 will be compared for Lu AF35700 versus active control using logistic regression with treatment as factor. The analysis will be done both for observed cases (OC) without imputation as well as for the whole FAS, imputing non-response (NRI) for missing observations at Week 8. The logistic regression model will be fitted using the maximum likelihood (ML) method and the logit link function. The odds ratios

for AF 35700 compared to risperidone/olanzapine will be estimated from the model and presented with p-values based on the likelihood ratio test and 95% CIs based on the profile likelihood.

12.5 Analysis of the Exploratory Endpoints

Change from Baseline 2 to Week 8 in BACS will be analyzed by analysis of covariance (ANCOVA). The model will include the fixed, categorical effects of treatment (Lu AF35700 and risperidone/olanzapine groups), strata (ED and LD) and fixed covariates of baseline scores (Baseline 1 and Baseline 2).

Change from Baseline 2 in PSP will be analyzed using the same methodology as that described for the primary endpoint (see section 12.3.1).

13 Safety

13.1 Adverse Events

13.1.1 General Methodology for Adverse Events

Summaries for Period A will be based on APTS_PC, and summaries for Period B will be based in APTS, respectively. Only stop-dates for ongoing events at Primary Outcome or Withdrawal Visit, and new SAEs are collected in the safety follow-up period. Therefore, adverse events in the safety Follow-up Period for non-randomized patients, and adverse events in the follow-up period for randomized patients will be included in summaries for Period A and Period B, respectively (periods are defined in section 13.1.4).

Tables by preferred term and tables by system organ class (SOC) and preferred term will be sorted in descending order by the percentage of patients in the total treatment group for Period A, and the Lu AF35700 treatment group in Period B.

Unless otherwise specified, the summaries of adverse events will include the number and percentage of patients with an adverse event.

If not otherwise stated, listings will be based on the APTS_PC and presented for all periods. Listings of adverse events will be sorted by site, treatment group (information about both treatment group in Period A and randomized treatment group will be included for randomized patients), patient screening number, and adverse event start date, and include preferred term, investigator term, period where AE has onset, adverse event start date, days since first IMP intake (days since first IMP in Period A and Period B will be included for randomized patients), duration of the adverse event, date of death, action taken, causality, intensity, seriousness, and outcome. For adverse events that change in intensity/seriousness, each intensity/seriousness will be included. Imputed adverse event start-or stop dates (see section 19.3.5) will be included in the listings, where information about the imputation will be included as a flag in the end of the date (M=month and day imputed or D=day imputed).

13.1.2 Coding of Adverse Events

Adverse events will be coded using MedDRA, version 20.0 or later.

13.1.3 Classification of Adverse Events

An adverse event will be classified as a Treatment Emergent Adverse Events (TEAE) according to the time of onset of the adverse event (for handling of incomplete start dates, see section 19.3.5):

Treatment-emergent adverse event (TEAE) - an adverse event that starts, or change from non-serious to serious, or increases in intensity compared to the preceding intensity at or after date of first IMP in Period A.

Handling of adverse events that increase in intensity or seriousness is further specified in section 19.4.2.

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

13.1.4 Allocation of TEAEs to Treatment Periods

Adverse events will be allocated to periods according to the date of onset of the adverse event (for handling of incomplete start dates, see section 19.3.5):

- *Screening Period* – an adverse event that starts before date of first IMP in Period A
- *Period A* - an adverse event that starts at or after the date of first IMP in Period A and at or before Visit 6 or Withdrawal Visit (non-randomized patients), or before date of first IMP in Period B (randomized patients).
- *Period B* - an adverse event that starts at or after the date of first IMP in Period B and at or before Visit 11 or Withdrawal Visit
- *Follow-up Period* - an adverse event that starts after last Visit in Period A (nonrandomized patients) or B (randomized patients)

13.1.5 Presentation of Adverse Events

All adverse events will be listed for the APES, including a flag for TEAE and indication of the period in which the AE started.

For each period an overview of the PYE, numbers, and percentages of patients with TEAEs, serious adverse events (SAEs), adverse events leading to withdrawal, and patients who died will be provided based on the APTS_PC and APTS respectively. For TEAEs, SAEs, and adverse events leading to withdrawal, the total number of events will be included.

13.1.6 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided for Period A and Period B:
- TEAEs by SOC and preferred term
- TEAEs by preferred term

The following summaries will be provided for Period B:
- TEAEs by sex and preferred term
- Causally related TEAEs by SOC and preferred term
- TEAEs by intensity *(mild/moderate/severe)*, and preferred term
- Causally related TEAEs by intensity, and preferred term

TEAEs with onset within the first 2 weeks in Period A based on APTS_A, and TEAEs within the first 2 weeks in Period B based on APTS will be presented by preferred term.

13.1.7 Presentation of Deaths

All adverse events for patients who died will be listed.

13.1.8 Presentation of Serious Adverse Events

All SAEs will be listed.

Treatment-emergent SAEs in Period A and Period B will be presented by:
- SOC and preferred term
- preferred term

13.1.9 Presentation of Adverse Events Leading to Withdrawal

All adverse events leading to withdrawal will be listed.

TEAEs leading to withdrawal in Period A and Period B will be summarized for
- SOC and preferred term
- preferred term

13.2 General Methodology for Other Safety Data

For details about data handling, see section 19.1, 19.2.1, and 19.2.2.

Summaries based on Period A will be based on the APTS_PC, and Period B based on the APTS.

The denominators for the summaries of a given variable will be based on the number of patients with non-missing values at a given week or during the assessment period. All

available post-Baseline 1/Baseline 2 assessments in the period will be included in the identification of the last assessment in a Period.

For patients with post-Baseline 1/Baseline 2 PCS values, listings will be provided including all available values for the variable, with flagging of PCS values and out-of-reference-range values.

All adverse events for patients with PCS values will be listed by treatment group and patient screening number and include the PCS value, the assessment date and the change from baseline (for the period) of the PCS value, the preferred term for the adverse event, start date, start period, and stop date of the adverse event. The PCS values and adverse events will be listed in chronological order according to assessment date and the start date of the adverse event.

If relevant, shift tables displaying shifts of out-of-the-reference range from Baseline 2 to any week in Period B will be provided for a test and include the numbers and percentages of patients.

For selected variables, the following graphical presentations may be provided:

- box plots by week and the last assessment
- patient line plots with all available assessments. Reference lines for reference ranges and/or PCS limits may also be included. If more than one value is available at a given assessment time point, the minimum/maximum value will be used in the plots.

13.3 Clinical Safety Laboratory Test Data

13.3.1 Data Presentation

The clinical safety laboratory test values will be presented either in conventional or Système International (SI) units. The PCS criteria for the clinical safety laboratory tests are shown in Appendix IV.

Descriptive statistics for the laboratory tests in Period A and Period B, both absolute values and changes from Baseline 1/Baseline 2, will be presented by test and week and the last assessment in the Period. The summaries for the absolute values will also include summaries for Baseline 1 and Baseline 2, respectively.

The number and percentage of patients with at least one PCS low value or PCS high value at any post-Baseline 1 assessment in Period A and at any post-Baseline 2 assessment in Period B will be summarized by test. All available assessments in the period will be included in the evaluation of PCS.

Non-fasting tests of S-Cholesterol, S-Glucose, S-HDL Cholesterol, S-LDL Cholesterol, and S-Triglycerides will be evaluated separately and only for PCS values.

Prolactin will also be presented by sex.

13.3.2 Potential Drug-induced Liver Injury (DILI)

Signals of DILI will be assessed according to the FDA guideline[2] using the following criteria:

- alanine aminotransferase (ALT) or AST >2×-, >3×-, 5×-, 10×-, or 20×ULN
- total bilirubin (BILI) >2×ULN
- alkaline phosphatase (ALP) >1.5×ULN
- ALT or AST >3×ULN AND BILI >1.5× or >2×ULN

In addition, assessment time points for patients for whom Hy's Law is potentially fulfilled will also be flagged in the listing (pHYL):

- ALT or AST >3 × ULN AND
- BILI >2xULN AND
- ALP<2

In the summaries, each patient should be counted only once using the maximum assessment, or the most severe for the combined criteria.

Patients fulfilling any of the individual criteria in Period B (ALT/AST, ALP, or BILI) will be listed, and the listing will include all available ALT, AST, BILI, and ALP, BILI, EOSLE, and GGT values (absolute and normalised), sorted by assessment date in ascending order. Evaluation of potential Drug-Induced Serious Hepatotoxicity (eDISH) will also be done by plots. Scatter plots of maximum ALT/AST versus maximum BILI will be presented for Period B. The criteria for the individual tests will be considered separately (that this means that the maximum of ALT/AST and the maximum BILI may not occur at the same assessment timepoint). The values will be normalised by the ULN (unit xULN) and the X-and Y-axes will be on the log scale. The plot will include a reference line for ALT/AST values >3xULN, and a reference line for BILI values >2xULN. Four quadrants are defined by the reference lines, where the right upper quadrant being the most specific indicator for a drug's potential for causing serious liver injury (Hy's law quadrant). The plot will include number of patients in each quadrant for each treatment group.

Subject line plots with values-by-time for ALT, AST, ALP, BILI, GGT and EOSLE (overlaid in the same plot) will be generated for patients with ALT/AST > 3xULN in Period B. The test values will be normalised by the ULN (unit xULN) and the Y-axis will be on the log scale. All assessments at Visit 6 or in Period B will be included, and the time will be days since first IMP in Period B. Reference lines for the day of first-and last IMP in Period B will be included. If there is more than one assessment at the same time point for a test, the maximum value will be used.

13.3.3 Changes in Fasting Lipid and Fasting Glucose Concentrations

Shift tables displaying the change in classification for fasting lipids and fasting glucose (Panel 2) from Baseline 2 to any visit in Period B will be provided for each test and include the numbers and percentages of patients. Note that only fasting tests will be considered.

Panel 2 Classification of Fasting Lipids and Fasting Glucose

Laboratory Test	Unit	Classification
Fasting S-triglycerides	mmol/L	Normal: 0.5-2.8; Borderline: >2.8 and < 4.2; PCS High: ≥ 4.2
Fasting total S-cholesterol	mmol/L	Normal: 3.2-5.2; Borderline: >5.2 and < 6.2; PCS High: ≥ 6.2
Fasting S-LDL cholesterol	mmol/L	Normal: 0.5-2.6; Borderline: >2.6 and < 4.9; PCS High: ≥ 4.9
Fasting S-HDL cholesterol	mmol/L	Normal: 0.9-1.6; PCS Low < 0.9
Fasting S- glucose	mmol/L	Normal: 4.5-5.6; Borderline: >5.6 and <7; PCS High: ≥7

13.4 Vital Signs and Weight

The PCS criteria for vital signs and weight are in Table 2.

Descriptive statistics for the body measurements (weight, BMI, and waist circumference) in Period A and Period B, both absolute values and changes from Baseline 1/Baseline 2, will be presented by variable and week and the last assessment in the Period. The summaries for the absolute values will also include summaries for Baseline 1 and Baseline 2, respectively.

Descriptive statistics for the vital signs parameters in Period B, both absolute values and changes from Baseline 2, will be presented by test and week and the last assessment in the Period. The summaries for the absolute values will also include summaries for Baseline 2.

The number and percentage of patients with at least one PCS low value or PCS high value at any post-Baseline 1 assessment in Period A and at any post-Baseline 2 assessment in Period B will be summarized by vital signs and body measurement parameter. All available assessments in the period will be included in the evaluation of PCS.

13.5 Electrocardiograms (ECGs)

The PCS criteria for the ECG parameters are in Table 3.

Descriptive statistics for the ECG parameters in Period B, both absolute values and changes from Baseline 2, will be presented by test and week and the last assessment in the Period. The summaries for the absolute values will also include summaries for Baseline 2.

The number and percentage of patients with at least one PCS low value or PCS high value at any post-Baseline 1 assessment in Period A and at any post-Baseline 2 assessment in Period B will be summarized by ECG parameter. All available assessments in the period will be included in the evaluation of PCS.

13.6 Other Safety Endpoints(s)

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

The Withdrawal Visit is windowed to a nominal visit according to the specification in section 19.2.2.

The C-SSRS was assessed at the following periods:

- for lifetime (using the Baseline/Screening Version) – the C-SSRS assessment obtained at screening that collects a lifetime recall
- in the past 3 months at screening (using the Baseline/Screening Version) – the C-SSRS assessment obtained at screening that focuses on the last 3 months
- at Baseline 1 (using the Since Last Visit Version) – the C-SSRS assessment obtained at Visit 2 that collects information from the Screening Visit to Visit 2
- Period A (using the Since Last Visit Version) – based on the C-SSRS assessments obtained after Visit 2 and at or before Visit 6
- Period B (using the Since Last Visit Version) – based on the C-SSRS assessments obtained after Visit 6 and at or before Visit 11
- Safety Follow-up (using the Since Last Visit Version) – based on the C-SSRS assessment obtained after last visit in Period A (non-randomized patients) or Period B (randomized patients)

For each period, it will be assessed whether the patient had *no suicidal ideation or behaviour* (patients that answered 'No' to all items in Panel 3 at visit(s) included in the period), and for each item in Panel 3 whether the most severe score (given by the ascending order in Panel 3) in the period was the item. *Non-suicidal self-injurious behaviour* is considered separately, and for each period it will be identified whether the patient had *non-suicidal self-injurious behaviour* (patients that answered 'Yes' to the item at any of the visit(s) included in the period). Missing C-SSRS scores will not be imputed.

For patients with any post-baseline suicidal behaviour (C-SSRS items 6 to 10), listings will be prepared including all C-SSRS scores based on the APES.

The derived C-SSRS items in each period will be summarized based on the APTS (data from the Safety Follow-up will only be included in the listing of patients with any post-baseline suicidal behaviour). The summaries will show the numbers and percentages of patients with *no suicidal ideation or behaviour,* the number and percentages of patients for each item for which the most severe score is the item, and number and percentages of patients with *non-suicidal self-injurious behaviour.*

Panel 3 C-SSRS Scores

C-SSRS Score		Related to:
1	Wish to be dead	Suicidal ideation
2	Non-specific active suicidal thoughts	
3	Active suicidal ideation with any methods (not plan) without intent to act	
4	Active suicidal ideation with some intent to act, without specific plan	
5	Active suicidal ideation with specific plan and intent	
6	Preparatory acts or behaviour	Suicidal behaviour
7	Aborted attempt	
8	Interrupted attempt	
9	Non-fatal suicide attempt	
10	Completed suicide (only applicable for the post-baseline assessments)	

14 Pharmacokinetic/Pharmacodynamic Analyses

A separate analysis plan for pharmacokinetic/pharmacodynamic analyses will be prepared by the Department of Quantitative Pharmacology, H. Lundbeck A/S.

15 Interim Analyses

No interim analysis is planned.

16 Sample Size Considerations

The sample size calculations as described in the protocol were as described below. As described in the preface, the study was prematurely stopped, and a total of 68 patients were randomized. Hence, the study is no longer powered to detect any of the mentioned difference. For reference, the protocol text is included below:

The sample size calculations are based on the US/Europe part of the study alone.

The study will include 75 randomized patients per group.

With 75 randomized patients per group in Period B, and assuming a common standard deviation of 18, there is approximately 80% power for showing a mean improvement in change in PANSS total score of 8 (standardized effect size 0.44) of Lu AF35700 over risperidone/olanzapine; with standard deviations of 16 and 20, there is approximately 86% and 70% power, respectively, to detect a difference of 8.

For the exploratory endpoint assessing efficacy in patients with ED TRS, with 50 randomized patients per group in Period B, and assuming a common standard deviation of 18, there is approximately 80% power for showing a mean improvement in change in PANSS total score

of 10 (standardized effect size 0.56) of Lu AF35700 over the active control; with standard deviations 16 and 20, there is approximately 87% and 70% power, respectively, to detect a difference of 10. The a priori assumption is that patients with ED TRS are a more homogeneous subgroup of patients with TRS than the overall TRS population and therefore will demonstrate a greater effect size for improvement in PANSS score.

Assuming an attrition rate of 40% in Period A, approximately 250 (=150/0.6) patients are expected to be enrolled to meet the target of randomizing 150 patients in Period B. The number of enrolled patients may be adjusted to meet the target of 150 randomized patients in the US/Europe part of the study.

In addition, it is planned to randomize approximately 20 patients from Japan. No formal sample size calculations have been performed for the Japanese cohort.

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 region, Period A treatment, 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.

No sample size re-assessment was performed.

17 Statistical Software

The statistical software used will be SAS®, Version 9.4 or later.

18 Changes to Analyses Specified in the Protocol

The statistical methodology section in the protocol describes that the following three populations will be evaluated upon:

1. US and Europe. This will be the study population
2. Japan
3. Pooled (US, Europe and Japan)

Only analyses based on the pooled population will be reported.

Period A treatment factor will not be included as a factor in the primary MMRM model. The rationale for the change is that the Period A treatment factor (olanzapine or risperidone) mixes up a pre-randomisation characteristic with the post-randomisation treatment received for those randomized to continued treatment. Thus it models a common difference between those that

receives different treatment (olanzapine or risperidone) in Period B with the difference in those receiving Lu AF35700 in Period B who were on olanzapine or risperidone in Period A. It seems unrealistic that the difference between the olanzapine and risperidone groups should be the same for those who continued to receive the olanzapine or risperidone treatment in Period B as it is for those who only received olanzapine or risperidone in Period A. For this reason the term "Period A treatment" should be removed from the model, both for the primary analysis and from all similar analyses based on MMRM as well as the logistic regression analyses.

It was planned to include region in the MMRM analysis. In total, 55 patients from Europe (Bulgaria and Russia), 6 from Japan and 7 from the USA were randomized. With this low numbers of patients, region is removed from all statistical models.

Due to the early termination of the study, and the reduced sample size, the analyses focusing on evaluating efficacy within/between early-in-disease and late-in-disease patient populations will not be performed. Hence the following endpoints will not be evaluated:

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)

The planned sensitivity analyses of the primary endpoint using Multiple Imputation Methods will not be performed.

For the responder analysis, the protocol stipulates a logistic regression model with Period A treatment, strata, region and treatment as factors and baseline PANSS total scores (Baseline 1 and Baseline 2) as covariates. Due to the reduced sample size, only treatment will be included as factor.

The protocol describes "Additional responder analyses using alternative cut-offs of the primary endpoint …". No such analysis will be performed.

The efficacy data collected after withdrawal from treatment were collected for a specific type of sensitivity analyses, which will no longer be performed. So the efficacy follow-up data collected will not be included in any efficacy analyses.

The relative time from Baseline 2 will be used in all displays related to Period B, i.e. Weeks 0, 1, 2, 4, 6 and 8 instead of Week 6, 7, 8, 10, 12, 14. This affects only terminology and does not change any of the specified analyses.

19 Details on Data Handling

19.1 Derived Variables

19.1.1 Missing Items

If ≤20% of the items are missing in the derivation of a variable based on a scale (see sections 19.1.2 to 19.1.6), the missing items will be imputed with the mean of the recorded items. The maximum number of missing items corresponding to ≤20% are specified in Panel 4. If more than 20% of the items are missing, the score will be missing.

Panel 4 Maximum Number of Missing Items on Rating Scales

PARAMCD	Description	Maximum Number of Missing Items
PANSSTOT	PANSS total score	6
POSITOT	PANSS Positive Symptom subscale score	1
NEGATOT	PANSS Negative Symptom subscale score	1
GENTOT	PANSS General Psyhopathology subscale score	3
FACNEG	PANSS Negative symptoms factor score	1
FACPOS	PANSS Positive Symptoms factor score	1
FACDISOR	PANSS Disorganized Thought factor score	1
FACUNC	PANSS Uncontrolled Hostility/Excitement factor score	0
FACANDEP	PANSS Anxiety/Depression factor score	0
NSA-16	16-item Negative Symptom Assessment	3
SWNSTOT	Subjective Well-being under Neuroleptics	4
BACS	Brief Assessment of Cognition in Schizophrenia (BACS)	1

19.1.2 PANSS

The PANSS[3] 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 consists of 30 individual items. Each item is rated from 1 (symptom not present) to 7 (symptom extremely severe).

The PANSS is grouped into three subscales: Positive Subscale Scores, Negative Subscale Score, and General Psychopathology Subscale Score. PANSS will also be grouped in five factor scores: Negative symptoms, Positive Symptoms, Disorganized Thought, Uncontrolled Hostility/Excitement, and Anxiety/Depression. The PANSS items and the derivation of the total score, the subscale scores, and the factor scores are described in Panel 5 and Panel 6.

Panel 5 PANSS Items and Subscales

PANSS Individual Item	PARAMCD	PANSS Individual Item	PARAMCD
Positive Scale		**General Psychopathology Scale**	
Delusions	PANSS01	Somatic concern	PANSS15
Conceptual disorganization	PANSS02	Anxiety	PANSS16
Hallucinatory behaviour	PANSS03	Guilt feelings	PANSS17
Excitement	PANSS04	Tension	PANSS18
Grandiosity	PANSS05	Mannerisms & posturing	PANSS19
Suspiciousness	PANSS06	Depression	PANSS20
Hostility	PANSS07	Motor retardation	PANSS21
Negative Scale		Uncooperativeness	PANSS22
Blunted Affect	PANSS08	Unusual thought content	PANSS23
Emotional withdrawal	PANSS09	Disorientation	PANSS24
Poor rapport	PANSS10	Poor attention	PANSS25
Passive-apathetic social withdrawal	PANSS11	Lack of judgement & insight	PANSS26
Difficulty in abstract thinking	PANSS12	Disturbance of volition	PANSS27
Lack of spontaneity & flow of conversation	PANSS13	Poor impulse control	PANSS28
Stereotype thinking	PANSS14	Preoccupation	PANSS29
		Active social avoidance	PANSS30

Panel 6 Derivation of PANSS total Score and Subscales

PANSS Total Score and Subscales	Derivation
PANSS Total Score	Sum of all items PANSS01 to PANSS30
PANSS Positive Symptom subscale score	Sum of items PANSS01 to PANSS07
PANSS Negative Symptom subscale score	Sum of items PANSS08 to PANSS14
PANSS General Psychopathology subscale score	Sum of items PANSS15 to PANSS30
PANSS Negative symptoms factor score	Sum of items PANSS08 to PANSS11, PANSS13, PANSS21, and PANSS30
PANSS Positive Symptoms factor score	Sum of items PANSS01, PANSS03, PANSS05, PANSS06, PANSS14, PANSS15, PANSS23, and PANSS26
PANSS Disorganized Thought factor score	Sum of items PANSS02, PANSS12, PANSS19, PANSS24, PANSS25, PANSS27, and PANSS29
PANSS Uncontrolled Hostility/Excitement factor score	Sum of items PANSS04, PANSS07, PANSS22, and PANSS28
PANSS Anxiety/Depression factor score	Sum of items PANSS16 to PANSS18, and PANSS20

In the calculation of percentage change in PANSS total score, 1 will be subtracted from each item (i.e. 30 subtracted from the total scores) in the calculation.[3] This transformation makes it possible to measure a change from the worst possible score to a complete absence of symptoms as a 100% change as the individual items ranges from 1 to 7 (e.g. if not doing the

subtraction, a change from the worst possible score of 210 to no lowest score corresponding to completely asymptomatic, the percentage change would be -86).

19.1.3 CGI

The CGI[4] severity of illness (CGI-S) is a clinician-rated scale.

CGI-S rates 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).

If CGI-S takes the value 0 (= not assessed) the score will be set to missing.

19.1.4 PSP

The PSP[5] is a clinician-rated scale designed and validated to measure a patient's current level of social functioning.

The PSP scale consists of a 100-point single-item rating scale, subdivided into 10 equal intervals. Scores of 1 to 10 indicate lack of autonomy in basic functioning, whereas scores of 91 to 100 reflect excellent functioning. The total score is rated by the investigator and is based on an algorithm which takes both the ratings of the 4 primary domains of PSP, and the combination of these ratings into account. The 4 primary domains are: socially useful activities (including work and study), personal and social relationships, self-care, and disturbing and aggressive behaviours. The 4 domains are assessed on a 6-point scale, from absent to very severe.

PSP Functional Remission is defined as a PSP total score ≥71. PSP Functional Response is defined as an improvement of at least 10 points of the PSP total score from Baseline.

The PSP domain D "Disturbing and aggressive behaviours" is categorized as "aggressive" (corresponding to 'Mild', 'Manifest', 'Marked', 'Severe', or 'Very Severe') and "non-aggressive" (corresponding to 'Absent').

19.1.5 16-item Negative Symptom Assessment (NSA-16)

The NSA-16[6] 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.

19.1.6 Subjective Well-being under Neuroleptics - Short Version (SWN-S)

The SWN-S[7] 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.

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

The BACS[8,9] 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 comprise 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.[10] The BACS is designed for use by clinical psychologists, neuro-psychologists, or clinicians with prior experience in administering cognitive tests in patients with schizophrenia.

19.1.8 Premorbid Adjustment Scale (PAS)

The PAS[11] 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.

19.2 Assigning Data to Visits, and Rules for Selecting Value at Visits

19.2.1 Laboratory Tests and ECG

Assessments at the Withdrawal Visit for patient withdrawn from treatment in Period A due to *Did not fulfil inclusion criteria for Period B* will be assigned to nominal Visit 6. Otherwise the assessments at the Withdrawal Visit and Unscheduled Visits (assessments not recorded at a scheduled visit) will be assigned to a nominal visit according to the visit windowing specified in Panel 7 and Panel 8. Note, assessments after Visit 2 for enrolled patients that did not have any IMP intake in Period A (i.e. enrolled patients not in APTS_PC) will be assigned to nominal Visit 1, and assessments after Visit 6 for randomized patients that did not have any IMP intake in Period B (i.e. randomized patients not in APTS) will be assigned to nominal Visit 6.

Panel 7 Visit Windows not Randomized Patients or at or before first IMP in Period B for Randomized Patients: Laboratory Tests and ECG

			Time Window (days)	
Nominal Visit Number	**Nominal Visit Week**	**Nominal Visit Day**	**Laboratory Tests**	**ECG**
V1	-3	-21	≤day of first IMP	≤day of first IMP
V4	2	14	day after first IMP - 28	NA
Not randomized patients				
V6	6	42	>28	>day of first IMP
Randomized patients				
V6	6	42	29 - day of first IMP in Period B	day after first IMP - day of first IMP in Period B

Panel 8 Visit Windows After first IMP in Period B Randomized Patients: Laboratory Tests and ECG

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V8	2	14	day after first IMP in Period B - 21
V9	4	28	22 – 42
V11	8	56	>42

Note that if the first IMP in Period A or Period B is the same day as the assessment, the assessment is assumed to be before the IMP intake.

Laboratory tests for which fasting is relevant (blood and serum tests for CDISC terms CHOL, GLUC, HDL, LDL, and TRIG) will have separate PARAM values in ADaM data, one for fasting and one for non-fasting/Unknown, and fasting and non-fasting/unknown assessments will be considered separately.

Baseline 1 will be the last assessment at or before Visit 2. If there is more than one assessment at the day of the last assessment, they will be ordered after date and time where assessment without recorded time will be considered to come after assessments recorded with time. The assessment last in the ordering will be used. If there is more than one assessment on the same date (and time), e.g. two assessments on the same date without recorded time, the maximum value will be used.

Baseline 2 will be the last assessment at or before Visit 6. If there is more than one assessment at the day of the last assessment, the Baseline 2 value will be selected using the same rule as for Baseline 1. For assessments recorded at Visit 6 that are after first IMP intake in Period B, the value will be considered as a valid Baseline 2 assessment if less than 7 days after the date of first IMP intake in Period B.

For last post-baseline assessment in Period A/Period B, the same ordering rule will be used as for baseline.

In analyses using visit, if there is more than one assessment at a nominal visit, the value will be selected using the following prioritization rule:

1. Scheduled Visit

If there is more than one assessment recorded at a scheduled visit, the one closest to the nominal day for the visit will be used in analyses using visit. If there are more than one assessment that are equally close to the nominal day, they will be ordered after date and time where assessment without recorded time will be considered to come after assessments recorded with time. The assessment first in the ordering will be used. If there is more than one assessment on the same date (and time), the maximum value will be used.

2. Withdrawal Visit or Unscheduled Visit

If there is more than one assessment, the value for analyses using visit will be selected using the same ranking as for multiple assessments at scheduled visits

Note, the visit value and baseline value may not be the same, e.g. if a patient has a scheduled assessment at Visit 1 and an unscheduled assessment at Visit 2 assigned to nominal Visit 1, the scheduled assessment at Visit 1 will be used as Visit 1 value, and the unscheduled assessment at Visit 2 will be used as Baseline 1 value.

Serum prolactin, HBA1c, and blood lipid profile are only scheduled to Visit 6 in Period A and Visit 11 in Period B, and the Withdrawal Visit will be assigned to Visit 6 for patients withdrawn from treatment in Period A and to Visit 11 for patients withdrawn from treatment in Period B.

19.2.2 Other assessments

For assessments only scheduled at Visit 6 in Period A, the Withdrawal Visit for patients withdrawn from treatment in Period A will be assigned to Visit 6. For assessments only scheduled at Visit 11 in Period B, the Withdrawal Visit for patients withdrawn from treatment in Period B will be assigned to Visit 11.

Assessments at the Withdrawal Visit for patient withdrawn from treatment in Period A due to *Did not fulfil inclusion criteria for Period B* will be assigned to nominal Visit 6. Otherwise, the assessment at the Withdrawal Visit for patients withdrawn from treatment in Period A and B will be assigned to a visit according to the windowing specified in Panel 9, Panel 10, and Panel 11.

Panel 9 Visit Windows Patients Withdrawn from Treatment in Period A: PANSS, CGI-S, C-SSRS, and Vital signs

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V1	-3	-21	NA
V2	0	0	NA
V3	1	7	Day after V2 - 11
V4	2	14	12-21
V5	4	28	22-35
V6	6	42	>35

Panel 10 Visit Windows Patients Withdrawn from Treatment in Period B: PANSS, CGI-S, C-SSRS, and Vital signs

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V6	0	0	NA
V7	1	7	Day after V6-11
V8	2	14	12-21
V9	4	28	22-35
V10	6	42	36-49
V11	8	56	>49

Panel 11 Visit Windows Patients Withdrawn from Treatment in Period B: PSP, NSA-16, SWN-S

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V6	0	0	NA
V9	4	28	day after V6-42
V11	8	56	>42

In analyses of efficacy (variables based on efficacy, exploratory, and Pharmaco-economic rating scales), if the Withdrawal Visit is assigned to the same visit as a scheduled visit, the assessments at the Withdrawal Visit will be used

For rating scales assessed at the Efficacy Follow-up Visit, the data from this visit will by definition be assigned to Visit 11 (Primary Outcome Visit). The follow-up efficacy data will only be used in a sensitivity analysis. In the sensitivity analysis, if there are more than one assessments assigned to the same visit, the value will be selected using the following prioritization order:

1. Efficacy Follow-up Visit
2. Withdrawal Visit
3. Scheduled Visit

In analyses of safety scales using visit, if the Withdrawal Visit is assigned to the same visit as a scheduled visit, the assessments at the Scheduled Visit will be used.

19.3 Handling of Missing or Incomplete Dates/Times

19.3.1 IMP Start and Stop Dates

A missing IMP start date for Period A will be imputed with the date of Visit 2, and a missing IMP start date for Period B will be imputed with the date of Visit 6.

A missing IMP stop date will not be imputed.

For enrolled patients, not in APTS_PC exposure will be set to 0, and for randomized patients not in APTS exposure in Period B will be set to 0. Exposure for patients in APTS_PC/APTS with missing IMP start-or stop date in Period A/Period B will not be calculated.

19.3.2 Lifetime Schizophrenia History

For the lifetime schizophrenia history, incomplete dates will be handled as follows. This applies both for calculating the duration of untreated psychosis and duration of treatment episodes:

- If only day is missing, this will be imputed to the 15th of the month
- If either start (first symptoms or start of treatment period) or end (first drug or end of treatment period) day is missing and start and end month and year are the same, the duration will be imputed to 15 days
- If day and month are missing for both start and end time, and end-year is not the same as start-year, duration will be imputed as difference in years
- If day and month are missing for both start and end time, and end-year is the same as start-year, duration will be imputed to 4 month. This is based on the average of all duration possibilities. E.g. if a patient start in January, he/she could end in January, February, …, or December, with possible durations of ½, 1½, 2½, …, 11½ months. A patient with start in February could end in February, March, … or December, with possible durations of ½, 1½, 2½, …, 10½ months. And so on, ending with a patient with start in December who can only have a duration of ½ month. Averaging these possibilities yields 4.17 months, which will be set as 4.
- A similar approach as above will be applied if only start-year is entered and end-year and month is entered (or vice versa). E.g. if end-month is February, then the duration can be 1½ month (if start month is January) or ½ month (if start month is February). The duration will be set to the average of these two possibilities = 1 month.

19.3.3 Medical Disorder Start and Stop Dates

Incomplete dates will not be imputed. Classification of events into *concurrent medical disorders* or *past disorders* will be based on the reported ongoing status.

19.3.4 Medication Start and Stop Dates

Imputation of incomplete or partially missing dates will be done in order to assigning the medication to the categories specified in section 9. No duration will be calculated for medications with imputed start-or stop date, or for ongoing medications.

Incomplete or missing medication dates will be imputed according to the algorithm below. If an imputed start date after this procedure is after the end date, the start date will be set to the end date.

- Patients in APTS_PC that are not randomized or randomized patients not in APTS:
  - *Incomplete start date where day is missing*

- If the start year and month are before the year and month of first IMP in Period A or after the year and month of the last visit in Period A (Visit 6 or Withdrawal Visit): date will be imputed with the medication start date assuming the day is the 1:st of the month
- If the start year and month are at or after the year and month of first IMP in Period A and at or before Visit 6 (including the withdrawal Visit): date will be imputed with the latest of medication start date assuming the day is the 1:st of the month, and the date of first IMP

- *Incomplete start date where month and day are missing*
  - If the year is equal to the year of first IMP in Period A: date will be imputed with the date of first IMP
  - If the year is before the year of first IMP, or after the year of Visit 6 (including the withdrawal Visit): date will be imputed with medication start date assuming the month and day are JAN the 1:st

- *Missing start date*
  The start date will be imputed with the date of first IMP in Period A

- Patients in APTS:
  - *Incomplete start date where day is missing*
    - If the start year and month are before the year and month of first IMP in Period A or after the year and month of Visit 11 or Withdrawal Visit: date will be imputed with the medication start date assuming the day is the 1st of the month

    - If the start year and month are at or after the year and month of first IMP in Period A and before year and month of the first IMP in Period B: date will be imputed with the latest of medication start date assuming the day is the 1st of the month, and the date of first IMP in Period A.

    - If the start year and month are at or after the year and month of first IMP in Period B and at or before Visit 11 or Withdrawal Visit: date will be imputed with latest of medication start date assuming the day is the 1st of the month, and the date of first IMP in Period B.

  - *Incomplete start date where month and day are missing*
    - If the year is equal to the year of first IMP in Period A and before the year of the first IMP in Period B: date will be imputed with the date of first IMP in Period A.

    - If the year is equal to the year of first IMP in Period B: date will be imputed with the date of first IMP in Period B.

- If the year is before the year of first IMP in Period A, or after the year of Visit 11 or Withdrawal Visit: date will be imputed with the medication start date assuming the month and day are JAN the 1st.

- *Missing start date*
  The start date will be imputed with the date of first IMP in Period B

Medication with incomplete end date where the day is missing, the date will be imputed with the minimum of the last day for the reported month and year and the end of study date. If month and day are missing for an end date, the date will be imputed with the minimum of medication end date assuming month and day are Dec 31, and the end of study date. If the medication end date is missing and the medication is not reported as ongoing, the end date will be imputed with the end of study date.

19.3.5 Adverse Event Start and Stop Dates

Imputation of partially missing dates will be done in order to classify the treatment-emergent status, and assigning the adverse event to a period. No duration will be calculated for adverse events with incomplete start-or stop date, or for ongoing adverse events.

Incomplete adverse start- and stop dates will be imputed before handling of incomplete dates for change in intensity- or seriousness (see section 19.4.2).

Incomplete adverse event start dates will be imputed according to the algorithm below. If an imputed start date after this procedure is after the adverse event end date, the start date will be set to the end date.

- Patients not in APTS_PC:
  - *Incomplete start dates where the day is missing*
    The start date will be imputed with the latest of adverse event start date assuming the day is the 1st of the month (e.g. if year=2017, and month=MAY, the start date would assume to be 01MAY2017), and date of Visit 1

  - *Incomplete start date where month and day are missing*
    The start date will be imputed with the latest of adverse event start date assuming the month and day are JAN the 1:st, and date of Visit 1

- Patients in APTS_PC that are not randomized or randomized patients not in APTS:
  - *Incomplete start date where day is missing*
    - If the start year and month are before the year and month of first IMP in Period A: the date will be imputed with the latest of adverse event start date assuming the day is the 1:st of the month, and Visit 1

    - If the start year and month are at or after the year and month of first IMP in Period A and at or before the last visit in Period A: date will be imputed with the latest

adverse event start date assuming the day is the 1:st of the month, and the date of first IMP

- If the start year and month are after the year and month of the last visit in Period A: date will be imputed with the latest of adverse event start date assuming the day is the 1:st of the month, and the day after last visit in Period A

- *Incomplete start date where month and day are missing*
  - If the year is equal to the year of first IMP in Period A: the date will be imputed with the date of first IMP

  - If the year is before the year of first IMP: the date will be imputed with the latest of adverse event start date assuming the month and day are JAN the 1st, and date of Visit 1

- Patients in APTS:
  - *Incomplete start date where day is missing*
    - If the start year and month are before the year and month of first IMP in Period A: date will be imputed with the latest of adverse event start date assuming the day is the 1:st of the month, and date of Visit 1

    - If the start year and month are at or after the year and month of first IMP in Period A and before first IMP in Period B: date will be imputed with latest of adverse event start date assuming the day is the 1st of the month, and the date of first IMP in Period A.

    - If the start year and month are at or after the year and month of first IMP in Period B and at or before last visit in Period B: date will be imputed with latest of adverse event start date assuming the day is the 1st of the month, and the date of first IMP in Period B.

    - If the start year and month are after the year and month of the last visit in Period B: date will be imputed with the latest of adverse event start date assuming the day is the 1:st of the month, and the day after last visit in Period B.

  - *Incomplete start date where month and day are missing*
    - If the year is equal to the year of first IMP in Period B: date will be imputed with the date of first IMP in Period B.

    - If the year is equal to the year of first IMP in Period A and before the year of the first IMP in Period B: date will be imputed with the date of first IMP in Period A.

- If the year is before the year of first IMP in Period A: date will be imputed with the latest of adverse event start date assuming the month and day are JAN the 1st, and date of Visit 1.

Adverse events with incomplete end date where the day is missing, the date will be imputed with the minimum of the last day in the reported month and year and the end of study date. If both month and day are missing for an end date, the date will be the minimum of adverse event end date assuming month and day are Dec 31, and the end of study date.

If the day in the date of intensity- or seriousness change is incomplete the date will be imputed using the same algorithm as for incomplete start date of adverse events but where the start date of the original event (that may have been imputed) or the preceding intensity if more than one intensity change is also taken into account. Three examples to illustrate this for a patient in APTS:

- If the adverse event start date of the original event was 15MAY2017, the date of first IMP in Period B 17MAY2017, and the incomplete date for change in intensity MAY2017, the change in intensity date would be imputed with the latest of 01MAY2017, 15MAY2017, and 17MAY2017, i.e. 17MAY2017.
- If the adverse event start date of the original event was 15MAY2017, the date of first IMP in Period B 02MAY2017, and the incomplete date for change in intensity MAY2017, the change in intensity date would be imputed with the latest of 01MAY2017, 15MAY2017, and 02MAY2017, i.e. 15MAY2017.
- If the adverse event start date of the original event was 15APR2017, the date of first IMP in Period B 13APR2017, and the incomplete date for change in intensity MAY2017, the change in intensity date would be imputed with the latest of 01MAY2017, 15APR2017, and 13APR2017, i.e. 01MAY2017.

If an imputed start date for an intensity change is after the end date for the original event, or after an intensity change that come after, the date of the intensity change will be set to the end date of the original event or the date of the intensity change that come after.

19.4 Data with Multiple Records

19.4.1 Medication Dose Changes

Dose changes or change in treatment regimen in concomitant medications are recorded on multiple rows in the eCRF, with different start and stop dates. When classifying medications into categories (see section 9), each record is considered as a separate medication, and the same drug name can be assigned to several categories for the same patient. Within a category, multiple entries will contribute as a single count in the summaries.

19.4.2 Adverse Events Changing in Intensity or Seriousness

Changes in adverse event intensity are included as additional rows in the ADaM data, where each change in intensity will be represented as an additional row, e.g. an adverse event that

changes from mild to moderate will have one additional row, one with intensity mild and one with intensity moderate (variable ASEV). The stop date for the intensity will be the stop date for the originally recorded event for the last intensity, and for the preceding rows the stop date will be set to the date of change in intensity minus 1 or the date of change if a change occurring on the same day as the originally reported event, or if there is more than one change on a day (for handling of incomplete dates, see section 19.3.5).

If the recorded start date of a serious adverse event is after the start date of the reported adverse event, the event is considered as having changed from non-serious to serious. Recorded seriousness for an adverse event will be the most serious (mapped to SDTM variable AESER, i.e. AESER=Y for an adverse event that change from non-serious to serious). In ADaM data, one additional row will be added for an adverse event that change from non-serious to serious, one with seriousness non-serious and one with seriousness serious (ADaM variable ASER). The stop date for the first row (ASER=N) will be the start date of the serious adverse event minus 1, and the stop date for the second row (ASER=Y) will be the stop date for the adverse event. After changed to serious, the adverse event is considered as serious onwards. If an intensity and seriousness is reported on the same date, rows will be added reflecting both the change in intensity and seriousness (e.g. for an adverse event originally reported as being mild and non-serious is reported as having changed to severe and serious on the same date, there will be one additional row in data).

Duration (days) will be calculated for each intensity/seriousness based on the intensity/seriousness start-and stop dates.

When classifying adverse events into periods, an event may be assigned to more than one period. An adverse event that changes in intensity or seriousness in a period will contribute to the count of events as one event in the summaries.

In summaries of adverse events presented by intensity, the maximum intensity of the adverse event will be used. The maximum intensity is searched for in events with changes, as well as over repeated events based on the preferred term. Adverse events for which information on intensity is missing will be classified as severe.

Adverse events for which information on seriousness is missing will be classified as *serious*.

References

1. Siddiqui O, Hung HMJ, O'Neill R. MMRM vs. LOCF: A comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat. 2009; 19: 227-246.
2. United States Food and Drug Administration (FDA). Guidance for Industry: Drug-induced liver injury: Premarketing Clinical Evaluation. July 2009.
3. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76
4. Haro JM, Kamath SA, Ochoa S, Novick D, Rele K, Fargas A, et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand. 2003; Suppl: 16-23.
5. Morosini P-L, Magliano L, Brambilla L et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatrica Scandinavica 2000; 101: 323-9
6. Alphs LD, Summerfelt A, Lann H, Muller RJ. The Negative Symptom Assessment: A new instrument to assess negative symptoms in schizophrenia. Psychopharmacology Bulletin. 1989; 25: 159-163.
7. Naber D, Moritz S, Lambert M, Pajonk F, Holzbach R, Mass R, et al. Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs. Schizophr Res. 2001; 50: 79-88.
8. Keefe, R.S.E., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M., Coughenour, L. The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophrenia Research. 2004; 68(2-3): 283-297.
9. Keefe, R.S.E, Poe, M., Walker T.M., Harvey P.D. The relationship of the Brief Assessment of Cognition in Schizophrenia (BACS) to functional capacity and real-world functional outcome. Journal of Clinical and Experimental Neuropsychology. 2006; 28: 260-269.
10. Keefe RSE, Harvey PD, Goldberg TE, Gold JM, Walker TM, Kennel C, et al. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res. 2008; 102: 108-115.
11. Cannon-Spoor HE, Potkln SG, Wyatt RJ. Measurement of Premorbid Adjustment in Chronic Schizophrenia. Schizophrenia Bulletin. 1982; 8(3): 470-484.

Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
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

SAP date: 13 March 2013

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

Authentication

Biostatistician: [redacted], Biostatistics

CRS: [redacted], Clinical Affairs & Operations

Authorization

Head of Biostatistics: [redacted]

Appendix II
Study Flow Chart

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)							√					√		

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
DAI-10 (PRO)							√					√		
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			√									√		

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
C-SSRS		√	√	√	√	√	√	√	√	√	√	√	√	
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 of the protocol. 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 protocol 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.]

Appendix III
SAS® Code

SAS® Code

Primary analysis

The SAS code for the primary analysis of the primary endpoint described in section 12.3.1 will be:

```
proc mixed data = xxx noclprint order = internal method = reml;
    class NOMWEEK2 STRATA TRT02P USUBJID;
    model CHG =    TRT02P STRATA NOMWEEK2 NOMWEEK2*TRT02P BASE1
                   BASE2 BASE1*NOMWEEK2 BASE2*NOMWEEK2 / ddfm = kr;
    repeated NOMWEEK2 / subject = USUBJID type = un;
    lsmeans NOMWEEK2*TRT02P / diff cl;
quit;
```

Appendix IV
PCS Criteria

PCS Criteria

Table 1 PCS Criteria for Clinical Safety Laboratory Tests

Laboratory Test	CDISC Term	Unit	PCS LOW	PCS HIGH
Haematology / Coagulation				
B-haemoglobin	HGB	g/dL	≤ 9.5 (women); ≤ 11.5 (men)	≥ 16.5 (women); ≥ 18.5 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women); ≤ 3.8 (men)	≥ 6.0 (women); ≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women); ≤ 0.37 (men)	≥ 0.50 (women); ≥ 0.55 (men)
B-MCV (mean cell volume)	MCV	fL	≤ 0.8 x LLN	≥ 1.2 x ULN
B-total leucocyte (white cell count)	WBC	x 10E9/L	≤ 2.8	≥ 16
B-neutrophils/leucocytes	NEUTLE	%	≤ 20	≥ 85
B-eosinophils/leucocytes	EOSLE	%		≥ 10
B-basophils/leucocytes	BASOLE	%		≥ 10
B-lymphocytes/leucocytes	LYMLE	%	≤ 10	≥ 75
B-monocytes/leucocytes	MONOLE	%		≥ 15
B-thrombocytes (platelet count)	PLAT	x 10E9/L	≤ 75	≥ 600
P-INR (prothrombin ratio)	INR	Ratio		≥ 2.0
B-prothrombin time	PT	Sec		≥ 18
Liver				
S-aspartate aminotransferase	AST	IU/L		≥ 3 × ULN
S-alanine aminotransferase	ALT	IU/L		≥ 3 × ULN
S-bilirubin	BILI	µmol/L		≥ 34
S-bilirubin, direct	BILDIR	µmol/L		≥ 12
S-bilirubin, indirect	BILIND	µmol/L		≥ 22
S-alkaline phosphatase	ALP	IU/L		≥ 3 × ULN
S-gamma glutamyl transferase	GGT	IU/L		≥ 200
S-alpha-glutathione S-transferase (alpha-GST)	GSTAL	µg/L		≥ 20
Kidney				
S-creatinine	CREAT	µmol/L		≥ 1.5 x ULN
B-urea nitrogen (BUN)	BUN	mmol/L		≥ 11
S-uric acid (urate)	URATE	µmol/L		≥ 510 (women); ≥ 630 (men)
Electrolytes				
S-sodium (natrium)	SODIUM	mmol/L	≤ 125	≥ 155
S-potassium (kalium)	K	mmol/L	≤ 3.0	≥ 6.0
S-calcium	CA	mmol/L	≤ 1.8	≥ 3.0
S-chloride	CL	mmol/L	≤ 90	≥ 117
S-magnesium	MG	mmol/L	≤ 0.6	≥ 1.3
S-phosphate (phosphorus, (inorganic)	PHOS	mmol/L	≤ 0.65	≥ 1.95
S-bicarbonate	BICARB	mmol/L	≤ 12	≥ 38
Endocrine / Metabolic				
B-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.4	≥ 9.4

Laboratory Test	CDISC Term	Unit	PCS LOW	PCS HIGH
B-glucose, fasting	GLUC	mmol/L	≤ 3.0	≥ 6.0
S-glucose, non-fasting/unknown	GLUC	mmol/L	≤ 3.9	≥ 11.1
S-glucose, fasting	GLUC	mmol/L	≤ 3.5	≥ 7.0
B-glycosylated haemoglobin, fasting	HBA1C	%		≥ 6.5
S-prolactin	PROLCTN	mIU/L		≥ 1350
S-thyrotropin/TSH	TSH	mIU/L	≤ 0.3	≥ 5.5
S-protein (total)	PROT	g/L	≤ 45	≥ 95
S-albumin	ALB	g/L	≤ 27	
Lipids				
S-cholesterol total, non-fasting/unknown	CHOL	mmol/L		≥ 7.8
S-cholesterol total, fasting	CHOL	mmol/L		≥ 6.2
S-triglycerides, non-fasting/unknown	TRIG	mmol/L		≥ 5.65
S-triglycerides, fasting	TRIG	mmol/L		≥ 4.2
S-LDL cholesterol, non-fasting/unknown	LDL	mmol/L		≥ 5.3
S-LDL cholesterol, fasting	LDL	mmol/L		≥ 4.9
S-HDL cholesterol, non-fasting/unknown	HDL	mmol/L	≤ 0.8	
S-HDL cholesterol, fasting	HDL	mmol/L	< 0.9	
Cardiac / Skeletal/Muscle				
S-creatine kinase (total)	CK	IU/L		≥ 400 (women); ≥ 750 (men)
S-creatine kinase MB isoenzyme	CKMB	µg/L		≥ 8.5 or
	CKMBCK	%		≥ 3.5% of total CK
S-lactate dehydrogenase (total)	LDH	IU/L		≥ 750
S-troponin I	TROPONI	µg/L		≥ 1.5
S-troponin T	TROPONT	µg/L		≥ 0.4
Infection				
S-C-reactive protein	CRP	mg/L		≥ 25
S-globulin (total)	GLOBUL	g/L	≤ 15	≥ 55
Urine				
Urinary pH	PH		≤ 4	≥ 9

S=serum; B=whole blood; U=urine

Table 2 PCS Criteria for Vital Signs, Weight/BMI and Waist Circumference

Parameter	CDISC Term	Unit	PCS LOW	PCS HIGH
Waist circumference	WSTCIR	Cm	decrease ≥ 7%	increase ≥ 7%
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure	OBP	mmHg	≤ -30	
Orthostatic pulse rate	OPR	beats/min		≥ 20
Temperature	TEMP	C	decrease ≥ 2	≥ 38.3 and increase ≥ 2

Increase/decrease is relative to the baseline value

Table 3 PCS Criteria for ECG Parameters

ECG Parameter	CDISC Term	Unit	PCS LOW	PCS HIGH
Absolute Time Interval				
PR interval	PRAG	Msec		≥ 260
QRS interval	QRSAG	Msec		≥ 150
QT interval	QTAG	Msec		≥ 500
Derived Time Interval				
Heart rate	EGHRMN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCBAG	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCFAG	Msec	< 300	> 500 or increase > 60

Increase/decrease is relative to the baseline value