Statistical Analysis Plan

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

Lu AF35700

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List of Abbreviations and Definitions of Terms

ADaM	Analysis Data Model
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APES	all-patients-enrolled set
APRS	all-patients-randomized set
APTS	all-patients-treated set
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BILI	Total serum bilirubin
CI	confidence interval
DILI	potential drug-induced liver injury
eCRF	electronic case report form
EPS	extrapyramidal symptoms
FAS	full-analysis set
GGT	gamma glutamyl transferase
ICH	International conference on harmonisation
IMP	investigational medicinal product
LLOQ	lower limit of quantification
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MNAR	missing not at random
NRI	non-response imputation
PCS	potentially clinically significant
PMM	Pattern-mixture model
PYE	patient years of exposure
QQ	quantile-quantile
rMI	reference-based multiple imputation
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SDTM	Study Data Tabulation Model
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TRS	Treatment resistant schizophrenia

1 Objectives

1.1 Primary Objective

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

1.2 Secondary Objective

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

1.3 Exploratory Objectives

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

1.4 Safety Objectives

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

2 Study Design

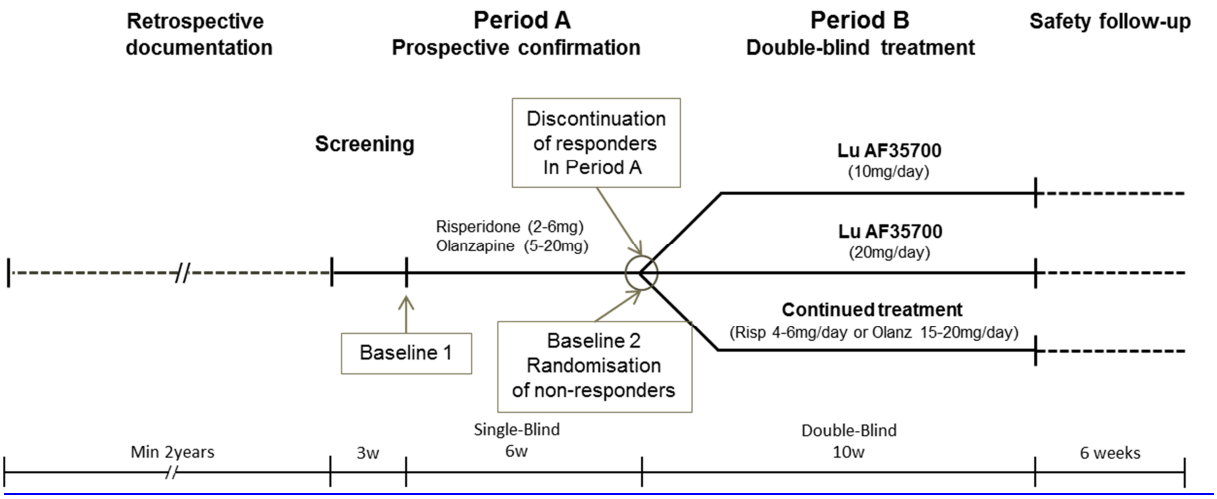
This is an interventional, multi-national, multi-site, randomized, double-blind, parallel-group, active-controlled, fixed-dose study.

This study will be conducted in compliance with the protocol, *Good Clinical Practice*,[1] and applicable regulatory requirements.

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.

A total of 675 patients (225 patients per treatment group) are planned to be randomized in Period B (randomization ratio 1:1:1 to Lu AF35700 10 mg, Lu AF35700 20 mg, or continued risperidone/olanzapine).

Panel 1 Study Design



The study includes a 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 (study Week 16) for the assessment of efficacy, safety and concomitant medication.

3 Definitions

3.1 Definition of Baseline

There are two baselines defined in this study (for details about data handling, see section 20.2):

Baseline 1 - the latest value captured at or before nominal Visit 2.

Baseline 2 (randomized patients) – for efficacy variables the latest value captured at or before nominal Visit 6, 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 is defined (see section 13.6.1).

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

3.2 Definition of Periods

Classification of adverse events into periods is defined in section 13.1.3.

For other data, assessments from the withdrawal visit and unscheduled visits will be assigned to a nominal visit (see section 20.2.1 and 20.2.2), 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* (10 weeks) - Starts after Visit 6 and continues up to, and including, Visit 12
- *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 20.1 and 20.2.2.

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 10 in PANSS total score*.

4.1 Primary Endpoint

Symptoms of schizophrenia (primary endpoint for primary objective)

4.2 Change from Baseline 2 to study Week 16 in PANSS total scoreKey Secondary Endpoints

Functioning (secondary objective)

- Change from Baseline 2 to study Week 16 in PSP total score

This endpoint is described as secondary in the protocol but has been promoted to key secondary endpoint and included in the testing strategy, see section 12.2.

4.3 Secondary Endpoints

Global clinical impression (supportive of primary objective)

- Change from Baseline 2 to study Week 16 in CGI-S score

Response at study Week 16 (supportive of primary objective)

- Response defined as ≥ 20% reduction in PANSS total score from Baseline 2, a PANSS total score of ≤ 70 and a CGI-S < 4
- Response defined as ≥20%, ≥30%, ≥40% and ≥50% reduction in PANSS total score from Baseline 2 (4 endpoints)

4.4 Exploratory Endpoints

Subjective well-being/quality of life and treatment satisfaction

- Change from Baseline 2 to study Week 16 in SWN-S total score
- Change from Baseline 2 to study Week 16 in MSQ score
- Change from Baseline 2 to study Week 16 in TooL total score
- Change from Baseline 2 to study Week 16 in QLS score

Symptoms of schizophrenia

- Change from Baseline 2 to study Week 16 in NSA-4 total score
- Change from Baseline 2 to study Week 16 in PANSS subscale scores (Negative Symptoms, Positive Symptoms and General Psychopathology)
- Change from Baseline 2 to study Week 16 in PANSS Marder factor scores (Negative symptoms, Positive Symptoms, Disorganized Thought, Uncontrolled Hostility/Excitement, and Anxiety/Depression)

4.5 Safety Endpoints

Safety and tolerability

- Adverse events
- Absolute values and changes from Baseline 2 in clinical safety laboratory tests, vital signs, weight, and ECG parameters
- Potentially clinically significant clinical safety laboratory test values, vital signs, weight, and ECG parameter values
- C-SSRS
- Change from Baseline 2 in mSAS, and AIMS total scores, and BARS Global Clinical Assessment of Akathisia score (item 4).

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 10 mg, LuAF35700 20 mg,, 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 2 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).

The efficacy data collected after withdrawal from treatment will be designated *efficacy follow-up data*. The efficacy follow-up data will only be used for sensitivity analyses performed for the FAS.

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 randomised treatment group will be included), patient screening number, sex, age, race, and weight at Baseline 1.

Disposition, demographics, demographics and other baseline characteristics based on APES or APTS_PC, and tables for Period A for recent and concomitant medications, exposure and compliance, adverse events, lab, and weight will be presented by Period A treatment group (risperidone and olanzapine) and in total. All other tables and figures for Period A will be presented for the total Period A treatment group.

Disposition, demographics, demographics and other baseline characteristics based on APRS or APTS, and tables and figures for Period B will be presented by randomized treatment group (LuAF35700 10 mg, LuAF35700 20 mg, and risperidone/olanzapine). Disposition, demographics, and baseline characteristics summaries will also be presented for the total treatment group, and safety tables for LuAF35700 in total.

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 chapter 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 inadequate treatment or plasma concentrations are described in chapter 11.

Patients who withdrew from treatment will be listed. The listing will be done by withdrawal from treatment in Period A and Period B. The listings will include the reason type (Primary reason for withdrawal from treatment, and Secondary reason for withdrawal from treatment), the reason, specification of other reason, date of Visit 2, date of randomisation, date of withdrawal from treatment, and number of days on IMP (IMP in Period A for non-randomised patients and IMP in Period A – IMP in Period B for randomised 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 (for handling of missing IMP start date, see section 20.3.1) 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, age group, race, and ethnicity), weight, BMI, and waist circumference at baseline 1, disease characteristics (age-and years since diagnosis of schizophrenia, years since first-and number of antipsychotic treatments, number of psychiatric hospitalisations), 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 summarised. CGI-S will be summarised both as a continuous and a categorical variable.

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 Seening Visit.

For patients in the APTS, relevant summaries will also be generated for patients who completed treatment and for patients who withdrew from treatment in Period B.

9 Recent and Concomitant Medications

9.1 All Recent and Concomitant Medications

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

Medications collected on the concomitant medication eCRF will be classified into categories according to the start and end date. Handling of missing or incomplete dates are specified in Section 20.3.3.

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 (randomised patients in APTS) or started before Follow-up Period (non-randomised patients and randomised 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 12 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 summarised by anatomical therapeutic chemical (ATC) code levels 2 and 3, and generic drug name. Medications started after Withdrawal Visit for Patients Withdrawn from Treatment in Period B and before the efficacy follow-up Visit will be summarised based on the FAS for patients with an efficacy follow-up Visit. The other categories will be summarised separately, where the first category will be based on the APTS_PC, and category two and three will be based on the APTS.

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.

9.2 Schizophrenia Treatment History for past 2 years and at Study Entry

All summaries and listings will be prepared based on the APTS_PC and APTS, respectively.

Schizophrenia Treatment History for past 2 years (except those taken within the last 91 days before entry into the trial which were to be recorded on the concomitant medication form) was recorded on a specific eCRF. The medications were collected in the corresponding way as on the concomitant medication eCRF, with additional information about evaluation of treatment response (improved, minimally improved, or not improved) for each of the reported treatments. Schizophrenia Treatment History for past 2 years will be summarised by ATC code levels 2 and 3, and generic drug name. Number and percentage of patients with at least one schizophrenia treatment leading to improvement will be summarised.

In addition, antipsychotics collected on the concomitant medication eCRF started before study start (Visit 1) will be classified as ongoing at study start or ended before study start. The categories will be summarised separately by ATC code levels 2 and 3, and generic drug name.

10 Exposure and Compliance

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

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

Compliance for Period 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:

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

End date period for Period A is Visit 6/Withdrawal visit (patient withdrawn from treatment in Period A) and for Period B Visit 12/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 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 summarised 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, PANSS General Psychopathology, and CGI-S at Baseline 1 and in Period A will be summarized by week and total therapy (risperidone and olanzapine) based on the FAS.

12 Efficacy and Pharmaco-economic

12.1 General Efficacy Analysis Methodology

For details about data handling, see section 20.1 and 20.2.2.

If not otherwise stated, the efficacy analyses will be based on the FAS. For all endpoints, the effects of the two doses of Lu AF35700 will be evaluated by testing the null hypothesis of no difference to the active control for each dose.

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 the endpoints not included in the testing strategy will be presented with nominal p-values and 95% CIs.

The efficacy data collected after withdrawal from treatment will be designated *efficacy follow-up data*. The *efficacy follow-up data* will only be used for one sensitivity analyses for the primary endpoint, as described in Section 12.3.1.

An addendum to the ICH E9 guideline on estimands and sensitivity analyses[2,3] is currently being developed. All efficacy endpoints will be analysed as pre-specified in the protocol. Endpoints involving PANSS total score will be put into the context of estimands. This is described in Section 12.7.

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, 8, and 10.

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

A multiple testing procedure will be applied on the testing of the two doses and the primary and key-secondary endpoints to control the overall type 1 error at 5%.

First the null hypothesis of no difference between each of the LuAF35700 doses compared to Risperidone/Olanzapine will be tested for the primary endpoint; change from baseline 2 to

week 16 in PANSS total score. A Hochberg's procedure will be used. In brief, this means that the p-values from the two tests Lu AF35700 20 mg versus Risperidone/Olanzapine and Lu AF35700 10 mg versus risperidone/olanzapine will be ordered in descending order. The largest p-value will be deemed statistically significant if less than 0.05. If significant, the smallest p-value will also be deemed statistically significant. If the largest p-value ≥ 0.05, the smallest p-value will be deemed statistically significant if this is < 0.025. If either is statistically significant, and the point estimate of the difference(s) favours Lu AF35700, Lu AF35700 will be deemed statistically significantly superior to risperidone/olanzapine.

Only if both Lu AF35700 10 mg and 20 mg are statistically significantly superior to Risperidone/Olanzapine for the primary endpoint, the test procedure will continue to test the null hypothesis of no difference between each of the LuAF35700 doses compared to Risperidone/Olanzapine for the key-secondary endpoint; change from baseline 2 to week 16 in PSP total score. A corresponding Hochberg's procedure as for the primary endpoint will be applied.

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

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 study Week 7, 8, 10, 12, 14, and 16, will be analyzed 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 (two doses of Lu AF35700 and active control), country, week, treatment-by-week interaction, Period-A-therapy (risperidone/olanzapine), Period-A-therapy-by-week interaction as well as the continuous, covariates of Baseline 2 score and baseline 2 score-by-week interaction. An unstructured (co)variance structure will be used to model the within-patient errors. If, unexpectedly, this analysis fails to converge, the following structures will be applied, in the following order: first-order ante-dependence, heterogeneous compound symmetry, compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The SAS code for the primary analysis is shown in Appendix III.

The primary comparisons will be the contrasts between each dose of Lu AF35700 and risperidone/olanzapine at the study Week 16 based on the least squares means for the treatment-by-visit interaction effect. The estimated mean difference between each dose and control based on this model will be reported with two-sided symmetric 95% confidence intervals and corresponding nominal p-value.

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 (country, visit, Period-A-therapy, treatment), and baseline 2 level of PANSS total score to account for differences in baseline 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 score, 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.[4]

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.

The plausibility of the missing-at-random (MAR) assumption will be investigated by visual inspection. To illustrate the missing data pattern, a plot with mean values-by-week will be presented, grouped by withdrawal pattern (week of last available value). At or before last available week, the mean values will be the mean of observed change from Baseline 2 (unadjusted) values. The mean values after last available week will be based on values predicted from the MMRM model in Section 12.3.1. Solid lines will indicate observed pattern, and dotted lines will indicate predicted pattern. The plot will include information about the number of patients for each withdrawal pattern. The plot will also be generated separately for each primary reason for withdrawal from treatment reported in more than 5% of the patients.

12.3.4 Sensitivity Analyses of the Primary Endpoint

Sensitivity analyses will be performed to evaluate how different assumptions affect the estimate of the treatment effects.

12.3.4.1 Sensitivity analysis using efficacy follow-up data

Individual subject-by-time (actual time) plots of the primary variable by primary reason for withdrawal from treatment or completion will be presented, including follow-up efficacy data. Data captured in the *treatment* period will be indicated with solid lines, and data captured in the withdrawal follow-up period will be indicated with dashed lines.

The same MMRM analysis as described for the primary endpoint(s) in Section 12.3.1 including efficacy follow-up data for patients withdrawn from treatment will be performed. The analysis will be based on the APTS. The number of patients for whom follow-up efficacy data have been collected will be summarized.

12.3.4.2 Sensitivity Analyses based on Multiple Imputation Methods

To assess the robustness of the study conclusions to the type of missing data in change in PANSS total score from Baseline 2 to study Week 16, analyses with different kinds of assumptions on the missing mechanism will be performed for data included in the primary analysis.

While the original analysis described in Section 12.3.1 assumes missing data to be MAR, sensitivity analyses will be performed to investigate different assumptions of MNAR for missing data after last available observation (e.g. if last available observation is at study week 12, data at study week 14 and 16 will be assumed to be MNAR).

Reference-based Multiple Imputation (rMI) method:

The reference-based multiple imputation (rMI) method assumes that the trajectory of patients with missing data from an experimental group is the same as that of the patients in the reference group, imputes an outcome almost certainly worse if the experimental group is more efficacious than that assumed by MAR, and is thus expected to be a stress test for MAR.

An analysis using a pattern-mixture model (PMM) will be performed, in which monotone missing values will be imputed using a sequential regression-based multiple imputation method, based on the imputation models established from the risperidone/olanzapine group.[5]

The procedure for the rMI method will include the following steps:

1. To prepare data for the rMI, intermittent missing values will be imputed using a Monte Carlo Markov Chain (MCMC) methodology assuming non-monotone missing values are missing at random. The imputation will be done by treatment group, and the model will include Baseline 2 PANSS total score, and change from baseline 2 in PANSS total score

at study week 7, 8, 10, 12, 14, and 16. The SAS® procedure proc MI will be used, using seed=19690325, and 200 imputations (nimpute=200).

2. Perform rMI on the monotone missing data created in step 1, where the monotone missing values are assumed to follow an MNAR pattern. The distribution for patients in the Lu AF35700 treatment groups at time t with last observation at time t-1, will be assumed to be equal to the conditional distribution for the risperidone/olanzapine group with the corresponding past. The regression model will include region, PANSS total score at Baseline 2 and changes from Baseline 2 in PANSS total scores, by using SAS® PROC MI using seed=19720203 and the MONOTON REG () option. A simpler model may be used, if the categories become too small.
3. Assemble a dataset containing data for all patients, including the imputed data from time t to serve as predictors for the imputation of missing data at the next week
4. Repeat steps 2) to 3) sequentially over all weeks (t+1, t+2…)
5. The 200 complete datasets will be analysed using the same MMRM model as described in section 12.3.1.
6. The estimated treatment effects and confidence intervals obtained across the imputed datasets will be combined to produce a unique point estimate and confidence interval using Rubin's rule to form a unique point estimate and standard error (SE), taking into account the uncertainty of the imputation[6], using SAS® PROC MIANALYZE.

Tipping point analysis with Delta-adjusting Multiple Imputation Method:

The departure from the MAR assumption will be investigated by progressively worsening the monotone missing values by assuming a MNAR pattern by an amount of delta (worsening) in the monotone missing observations. An analysis will be performed using a pattern-mixture model (PMM), in which monotone missing values in the AF35700 treatment groups will be imputed using a sequential regression-based multiple imputation method, based on delta-adjusting multiple imputation.[7]

A series of this delta-adjustment analysis will be performed with a range of increasing δ values for providing a progressively more severe stress test to assess how extreme departures from MAR would need to be to overturn the primary result. The values of δ will start from 0%, 10%, 20%, ..., and up to 100% of the treatment difference at the visit where this delta-adjustment applies, which is estimated using the MMRM analysis, such that the absolute adjustment may vary with visits. This procedure continues until δ =100% or a "tipping point" of δ is achieved that overturns the primary result, whichever comes first. A judgement as to the credibility of the primary results can then be informed from a clinical point of view, by assessing the plausibility of the adjustment that is needed to nullify the primary result.

The procedure for the delta-adjusting multiple imputation method will include the following steps for each value on delta:

1. Impute missing intermittent data by using the same methodology and seed as in step 1 for the rMI.
2. At time t, perform regression-based multiple imputations on the monotone missing data created in step 1. The regression model will include region, treatment group, PANSS total

score at Baseline 2 and changes from Baseline 2 in PANSS total scores, by using SAS® PROC MI using seed=19720203 and the MONOTON REG () option. A simpler model may be used, if the categories become too small.

3. After imputation at time t, for patients in the AF35700 treatment groups, make the imputed value at each visit after last available value worse by a value of δ. For the PANSS total score, it means adding δ to the imputed value.
4. Impute all remaining time-points sequentially by repeating steps 2 and 3 for each time-point, incorporating the imputed and delta-adjusted values from the previous step as predictors in the imputation model for the next time-point.
5. The 200 complete datasets will be analysed using the same MMRM model as described in Section 12.3.1.
6. The estimated treatment effects and confidence intervals obtained across the imputed datasets will be combined to produce a unique point estimate and confidence interval using Rubin's rule to form a unique point estimate and standard error, taking into account the uncertainty of the imputation.[8]

For each delta, a plot with mean change from Baseline 2 values-by-week will be presented, grouped by week of last available value. At or before last available week, the mean values will be the mean of observed (unadjusted) values. The mean values after last available week will be based on values imputed from the PMM (observations assumed to be MNAR). Solid lines will indicate observed pattern, and dotted lines will indicate imputed/predicted pattern. The plot will include information about the number of patients for each group.

12.3.4.3 Sensitivity Analysis Model without Period A Treatment

A sensitivity analysis excluding Period A therapy from the model in 12.3.1 will be performed, i.e. a model including fixed, categorical effects of treatment (two doses of Lu AF35700 and active control), country, week, treatment-by-week interaction, as well as the continuous, covariates of Baseline 2 and Baseline 2 score-by-week interaction.

12.3.4.4 Sensitivity Analysis Using Values with Measurable Plasma Concentration

An analysis using the same model as specified in Section 12.3.1, excluding observations with plasma concentrations ≤ LLOQ of LuAF35700/risperidone/olanzapine will be performed. For instance, if a patient has measurable values at study Week 7, 8, 10, 12, and 16, but not at Week 14, the value at Week 14 will be excluded.

12.3.5 Covariate Investigation and Subgroup Analyses for the Primary Endpoint

Covariates that will be investigated are

- age
- years since diagnosis
- number of antipsychotic treatments
- age at onset of schizophrenia

- number of previous psychiatric hospitalizations

The potential influence of covariates will be investigated using an MMRM model similar to the one specified in Section 12.3.1 by adding main terms for covariates and interaction terms with treatment and week to the model. The p-value for the test of difference in the average effect of LuAF35700 10- and 20 mg compared to risperidone/olanzapine for the covariate at Week 16 will be presented.

Subgroups that will be investigated are

- region: US/Canada, Europe, and Rest of the World
- sex
- age: <35, 35-49, and ≥ 50 years
- race: white, and other
- years since diagnosis: ≤5, 6-9, and ≥10 years

When considered relevant, the covariate analyses may lead to further subgroup analyses.

For the subgroups, analysis will be performed by category separately, using the same methodology as that described for the analysis of the primary endpoint (see paragraph 12.3.1), except for region where country will be excluded from the model.

The assumption of equal treatment effect across subgroups will also be investigated for region, sex, and race by adding the three way interaction *subgroup*-by-treatment-by-week to the model in the analysis of the primary endpoint (see paragraph 12.3.1). The treatment effect for each dose of LuAF35700 compared to risperidone/olanzapine in each category of the subgroup will be estimated by least square means for the contrast *subgroup*-by-treatment-by-week. Furthermore, the p-value for the test of difference in the average effect of LuAF35700 10-and 20 mg compared to risperidone/olanzapine for the subgroups at Week 16 will be presented. In the test of region, the test will be performed for Europe compared to Other regions (US/Canada/Rest of World).

Selection of subgroups based on population pharmacokinetic analysis will be reported separately.

12.4 Analysis of the Key Secondary Endpoints

The testing strategy for the key secondary endpoint, change from Baseline 2 to study Week 16 in PSP total score, is described in Section 12.2.

The key-secondary endpoint will be analysed using the same methodology as that described for the primary endpoint, see section 12.3.1.

12.5 Analysis of the Secondary Endpoints

Change from Baseline 2 to study Week 16 in CGI-S score will be analyzed using the same methodology as that described for the primary endpoint (see section 12.3.1).

The proportion of patients responding at study Week 16 will be compared for each dose versus active control using logistic regression with Region (US/Canada, Europe, and Rest of the World) and treatment as factors. The analysis will be done for observed cases (OC) as well as for the whole FAS, imputing missing values as non-response.

Response is defined as ≥ 20% reduction in PANSS total score from Baseline 2, a PANSS total score of ≤ 70 and CGI-S score < 4. 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 20.1.

Additional responder analyses of ≥20%, ≥30%, ≥40% and ≥50% reduction in PANSS total score from Baseline 2 to study Week 16 will be presented using the same methodology.

The logistic regression model will be fitted using the maximum likelihood (ML) method and the logit link function.

The odds ratios for AF 35700 10 and 20 mg 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.

12.6 Analysis of the Exploratory Endpoints

Change from Baseline 2 to study Week 16 in NSA-4, SWN-S, MSQ, TooL and QLS total scores, and change from Baseline 2 to study Week 16 in PANSS subscale-and Marder factors will be analyzed using the same methodology as that described for the primary endpoint (see section 12.3.1).

12.7 Estimands

As mentioned in Section 12.1, an addendum to the ICH E9 guideline on estimands and sensitivity analyses is currently being developed. This section will describe the planned analyses in the context of this draft guideline. Only analyses involving the primary efficacy parameter (PANSS total score) will be described.

An estimand is the target of estimation to address the scientific question of interest posed by the trial objective. Attributes of an estimand include:

a) the **population** of interest
b) the **variable** (or endpoint) of interest
c) the specification of how **intercurrent events** are reflected in the scientific question of interest
d) the population-level **summary** for the variable

The only **intercurrent events** considered will be withdrawal from treatment in Period B. As described in Section 12.3.4, all reasons for withdrawal will be handled in the same way.

The primary objective is:

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

The primary endpoint is:

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

Panel 2 below summarizes the estimands that are addressed by the study.

Panel 2 Estimands

Endpoint (as described in earler sections)	**Estimand attributes**				**Analysis**
	Population	**Variable**	**Intercurrent events strategy**	**Summary**	
Primary endpoint	As defined in inclusion and exclusion criteria and who continue treatment to completion	Change from Baseline 2 to study Week 16 in PANSS total score	**Hypothetical**: What is the effect if patients continue treatment until completion.	Mean difference at study Week 16	MMRM
Sensitivity: Primary endpoint + efficacy follow-up	As defined in in and exclusion criteria	Change from Baseline 2 to study Week 16 in PANSS total score	**Treatment policy**: What is the effect regardless of which/any treatment patients initiate after withdrawal. (In principle, this strategy cannot be implemented when values for the efficacy follow-up visit do not exist for all withdrawn patients)	Mean difference at study Week 16	MMRM
Sensitivity: rMI	As defined in in and exclusion criteria	Change from Baseline 2 to study Week 16 in PANSS total score	**Treatment policy**: What is the effect if withdrawn patients start on antipsychotic medication.	Mean difference at study Week 16	MMRM
Sensitivity: Tipping point/Delta	As defined in in and exclusion criteria	Change from Baseline 2 to study Week 16 in PANSS total score	Robustness analysis (**treatment policy**). A delta value of 0% corresponds to a missing at random assumption, while 100% corresponds to rMI.	Mean difference at study Week 16	MMRM
Adherence (adequate plasma concentrations)	As defined in in and exclusion criteria and patients that adhere to	Change from Baseline 2 to study Week 16 in PANSS total score	**Hypothetical**: What is the effect if patients adhere to the randomized treatment regimens until completion.	Mean difference at study Week 16	MMRM

	treatment and remain in the study				
Response, NRI	As defined in in and exclusion criteria	Percentage change from Baseline 2 at study Week 16 in PANSS total score ≤ -20% and PANSS total score ≤ 70 and CGI-S < 4	**Composite**: Withdrawal is part of the endpoint definition, as patients withdrawn from treatment are set as non-responders	Odds ratio at study Week 16	Logistic regression

The rationale for choosing MMRM for the primary analysis is described in Section 12.3.2. The primary analysis of the primary endpoint focuses on the obtained pharmacological effect of Lu AF35700 versus antipsychotic medication, i.e. the effect that can be expected if the randomized treatment is taken as prescribed in the prescribed period. This is considered a relevant measure to evaluate the efficacy/effectiveness of treatment in schizophrenia.

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.

In addition to the analyses presented in Panel 2, a responder analysis using observed data was specified in the protocol (see Section 12.5).

12.8 Pharmaco-economic

HEA items will be summarized for Baseline 2 and visits in Period B based on the APTS. When relevant, changes from Baseline 2 will also be presented by visit in Period B.

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 follow-up period. Therefore, adverse events in the Follow-up Period for non-randomised patients, and adverse events in the follow-up period for randomised 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 20 mg 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 randomised treatment group will be included for randomised patients), patient screening number, and adverse event start date, and include preferred term, investigator term, period, adverse event start date, days since first IMP intake (days since first IMP in Period A and Period B will be included for randomised 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 20.3.4) 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 20.3.4):

- *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 first IMP in Period A

Handling of adverse events that increase in intensity or seriousness is further specified in section 20.4.2.

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 Adverse Events to 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 20.3.4):

- *Screening Period* – and adverse event that starts before first IMP in Period A

- *Period A* – an adverse event that starts at or after the first IMP in Period A and at or before Visit 6 or Withdrawal Visit (non-randomised patients), or before first IMP in Period B (randomised patients).
- *Period B* – an adverse event that starts at or after the first IMP in Period B and at or before Visit 12 or Withdrawal Visit
- *Follow-up Period* – an adverse event that starts after last Visit in Period A (non-randomised patients) or B (randomised 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
- TEAEs with an incidence ≥2% and ≥5% in any treatment groups by 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 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 summarised by
- SOC and preferred term
- preferred term

13.2 General Methodology for Other Safety Data

For details about data handling, see section 20.1, 20.2.1, and 20.2.2.

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 worst value (depending on the parameter maximum or minimum 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[9] 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 3) 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 3 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

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 20.2.2.

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 since 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 12
- Safety Follow-up (using the Since Last Visit Version) – based on the C-SSRS assessment obtained after last visit in Period A (non-randomised patients) or Period B (randomised patients that do not continue into the 16159B study)

For each period, it will be identified if the patient had *no suicidal ideation or behaviour* (patients that answered 'No' to all items in Panel 4 at visit(s) included in the period), and for each item in Panel 4 whether the most severe score (given by the ascending order in Panel 4) 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 Period A will be summarised based on the APTS_PC, and for each Period 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 4 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)	

13.6.2 EPS Rating Scales

For details about data handling, see section 20.1 and 20.2.2.

Absolute and change from Baseline 2 in AIMS total score, mSAS total score, and BARS Global Clinical Assessment of Akathisia score (item 4) will be summarised at by week in Period B based on the APTS (Baseline 2 will also be included in the summaries of the absolute scores). The maximum change to Baseline 2 in Period B will also be summarised.

In addition, the BARS Global Clinical Assessment of Akathisia will be presented with descriptive tables showing number and percentage of patients in each category for Baseline 2 and by week in Period B based on the APTS.

The single-item scores for AIMS items 8 to 12 and BARS items 1, 2, and 3 will be summarized by Baseline 2 and week in Period B based on the APTS

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 Blinded Data Reviews

As described in the protocol, a blinded re-assessment of sample size will be performed when 50% of the patients have completed the treatment period. The blinded re-assessment was included briefly in the original protocol, and the detailed description repeated in this section was introduced in Protocol amendment 1, which was finalized May 16, 2016 before the first patient was randomized.

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 the treatment, i.e. the following:

The model will include the fixed, categorical effects of country, week, Period-A-therapy (risperidone/olanzapine), Period-A-therapy-by-week interaction as well as the continuous, fixed covariates of baseline 2 score and baseline 2 score-by-week interaction.

A short memo of the blinded sample size re-assessment will be prepared. All data will be kept blinded, and hence it is considered to have no effect on the significance or on the conduct of the study.

16 Interim Analyses

No interim analysis is planned.

17 Sample Size Considerations

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

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

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

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

18 Statistical Software

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

19 Changes to Analyses Specified in the Protocol

The change from Baseline 2 to study Week 16 in PSP total score has been promoted from secondary to key secondary endpoint, and a testing strategy defined.

The logistic regression model for analysis of response at Week 16 was simplified and only included factors for region and treatment (two doses of Lu AF35700 and active control) in order to avoid convergence issues.

Responder analyses of % change in PANSS total score using cut-points of 20%, 30%, 40%, and 50% reduction in PANSS total score from Baseline 2 to study Week 16 were added as secondary endpoints, using the same methodology as for the response at Week 16.

Change from Baseline 2 to study Week 16 in PANSS Marder factor scores (Negative symptoms, Positive Symptoms, Disorganized Thought, Uncontrolled Hostility/Excitement, and Anxiety/Depression) were added as exploratory endpoints. The change from Baseline 2 in PANSS factor scores were analysed with the same methodology as for the primary endpoint (see section 12.3.1).

The change from Baseline 2 in AIMS total score, BARS Global Clinical Assessment of Akathisia score (item 4), and WoRQ will only be summarised descriptively.

In addition to the analyses described in the protocol, the change from Baseline 2 to study Week 16 for the PANSS subscale scores have been added as exploratory endpoints.

20 Details on Data Handling

20.1 Derived Variables

20.1.1 Missing Items

If ≤20% of the items are missing in the derivation of a variable based on a scale (see sections 20.1.2 to 20.1.12), the missing items will be imputed with the mean of the recorded items

except for NSA-4 where no missing items are allowed since the global score has a different range. The maximum number of missing items corresponding to ≤20% are specified in Panel 5. If more than 20% of the items are missing, the score will be missing.

Panel 5 Maximum Number of Missing Items on Rating Scales

PARAMD	Description	Maximum Number of Missing Items
PANSSTOT	PANSS total score	6
POSITOT	PANSS Positive Symptoms	1
NEGATOT	PANSS Negative Symptoms	1
GENTOT	PANSS General Psyhopathology	3
FACNEG	PANSS Negative symptoms Marder factor score	1
FACPOS	PANSS Positive Symptoms Marder factor score	1
FACDISOR	PANSS Disorganized Thought Marder factor score	1
FACUNC	PANSS Uncontrolled Hostility/Excitement Marder factor score	0
FACANDEP	PANSS Anxiety/Depression Marder factor score	0
NSATOT	NSA-4 total score	0
SWNSTOT	Subjective Well-being under Neuroleptics	4
TOOLTOT	Tolerability and Quality of Life Total Score	1
QLSTOT	Quality of Life Scale	4
SASTOT	Simpson-Angus Scale (SAS) total score	2
AIMSTOT	Abnormal Involuntary Movement Scale (AIMS) total score	1

20.1.2 PANSS

The PANSS[10] 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 Marder factor scores are described in Panel 6 and Panel 7.

Panel 6 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 7 Derivation of PANSS total Score, Subscales, and Marder Factor Scores

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 Marder factor score	Sum of items PANSS08 to PANSS11, PANSS13, PANSS21, and PANSS30
PANSS Positive Symptoms Marder factor score	Sum of items PANSS01, PANSS03, PANSS05, PANSS06, PANSS14, PANSS15, PANSS23, and PANSS26
PANSS Disorganized Thought Marder factor score	Sum of items PANSS02, PANSS12, PANSS19, PANSS24, PANSS25, PANSS27, and PANSS29
PANSS Uncontrolled Hostility/Excitement Marder factor score	Sum of items PANSS04, PANSS07, PANSS22, and PANSS28
PANSS Anxiety/Depression Marder 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.[10] 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).

20.1.3 CGI

The CGI[11] 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.

20.1.4 PSP

The PSP[12] 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').

20.1.5 4-item Negative Symptom Assessment (NSA-4)

The NSA-4[13] is a clinician rated scale designed to assess the severity of negative symptoms of schizophrenia. It consists of 4 items to measure: restricted speech quantity, reduced emotion, reduced social drive, and reduced interests, as well as an overall global rating of negative symptoms. Each of the four items is rated on a 1 to 6-point scale where '1' represents no reduction from normal behaviours associated with the item and '6' represents severe reduction or absence of the behaviour. The scale also includes a "non ratable" designation denoted as '9'. The global rating of negative symptoms ranges from 1 to 7.

The total score is the sum of the 4 items and the global score. In the derivation of the total score, an item recorded as 9 will be treated as a missing value. The total score ranges from 5 to 31.

20.1.6 Tolerability and Quality of Life (TOOL)

The TooL[14] a patient-rated scale developed to measure the impact of side-effects on the quality of life in patients treated with antipsychotic medication. The TooL consists of eight domains: mood (worry-upset), function capabilities, fatigue-weakness, weight gain, stiffness-tremor, physical restlessness, sexual dysfunction and dizziness-nausea. Each domain is rated on a 4-point scale from 1 (no impact) to 4 (maximum impact). Total scores range from 8 (no impact) to 32 (maximum impact).

20.1.7 Subjective Well-being under Neuroleptics - short version (SWN-S)

The SWN-S[15] 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.

20.1.8 Medication Satisfaction Questionnaire (MSQ)

The MSQ[16] is a patient-rated scale designed and validated to assess the patient's satisfaction with his or her current antipsychotic medication. The MSQ consists of one item that is rated on a 7-point scale ranging from 1 (extremely dissatisfied) to 7 (extremely satisfied). The patient can complete the MSQ without any training.Quality of Life Scale (QLS)

The QLS[17] is a clinician-rated scale designed to assess intrapsychic, social, and negative symptoms of schizophrenia and their consequences for functioning during the preceding 4 weeks. The QLS consists of 21 items in 4 subscales: Interpersonal Relations (items 1 to 8), Instrumental Role (items 9 to 12), Intrapsychic Foundations (items 13 to 18, and 20 to 21), and Common Objects and Activities (items 18 and 19). Each item has a brief description of the judgement to be made and a set of suggested probes for the clinician. Each item is rated on a 7-point scale, from 0 (severe impairment) to 6 (normal or unimpaired functioning). Definitions are provided for 4 anchor points of the 7 points. The mean score is calculated for each subscale. The total score is the sum of all items, and ranges from 0 to 126, where the higher score indicates normal or unimpaired functioning.

Note, if item 1 is rated 9, protate in the calculation of Interpersonal Relations subscale score and the total score are based on items 2-8. If item 9 is rated less than 3, item 12 should be rated as 9=Not applicable and protate in the calculation of the Instrumental Role subscale score and total score are based on items 9 to 11. Note, item 1 or 12 recorded as 9 are not counted as missing items in the calculation of the total score (see Panel 5).

20.1.9 Readiness for Work Questionnaire (WoRQ)

The WoRQ[18] a clinician-rated scale designed to measure readiness to work in patients with schizophrenia. The WoRQ consists of 8 items: the clinician must rate 7 statements and answer one question. The statements are rated on a 4-point scale, from *strongly agree, agree, disagree* or *strongly disagree* based on all material available (for example, personal notes, medical records, input from other health professionals, family members or caregivers); and in the final item, the clinician must indicate if the patient ready for work or not. The WoRQ can be rated by a clinician after a short training session.

20.1.10 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[19] is a clinician-rated scale designed to assess abnormal involuntary movements (for example, dyskinesia) associated with anti-psychotic drugs. The AIMS consists of 12 items: items 1 to 7 assess the severity of movements in 3 anatomical areas (facial/oral, extremities and trunk); items 8 and 9 assess the global severity and the incapacitation due to the movements; item 10 assesses the patient's awareness of the movements and the distress due to them; items 11 and 12 clarify the patient's dental status. The 12 items are assessed using a neurological examination: items 1 to 9 are rated on a 5-point scale, from 0 (none) to 4 (severe); item 10 is rated on a 5-point scale, from 0 (no awareness) to 4 (aware, severe distress); and items 11 and 12 are rated yes/no. The AIMS Total Score is the sum of item 1 to 7 and ranges from 0 to 28.

20.1.11 Barnes Akathisia Scale (BARS)

The BARS[20] is a clinician-rated scale designed to assess the presence and severity of druginduced akathisia. The BARS consists of 4 items: one objective item (observed restlessness), two subjective items (patient's awareness of restlessness and related distress), and a global clinical assessment of akathisia. The objective and subjective symptoms are rated on a 4-point scale, from 0 (no symptom) to 3 (severe symptoms). The global clinical assessment is rated on a 6-point scale from 0 (absent) to 5 (severe akathisia).

20.1.12 Simpson Angus Scale (SAS)

The SAS[21] is a clinician-rated scale designed to assess the presence and severity of druginduced parkinsonism. A modified version of the SAS will be used consisting of 10 items to evaluate gait, rigidity (arms, head and legs), tremor, salivation and akathisia. The 10 items are assessed using a neurological examination and rated on a 5-point scale, from 0 (absence of the condition) to 4 (most extreme form of the condition). Comprehensive definitions are provided for each anchor point on the scale. The SAS Total Score is the sum of all 10 items and ranges from 0 to 40.

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

20.2.1 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 8 and Panel 9. Note, assessments after Visit 2 for enrolled patients that didn't had 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 didn't had any IMP intake in period B (i.e. randomized patients not in APTS) will be assigned to nominal Visit 6.

Panel 8 Visit Windows not Randomised Patients or at or before first IMP in Period B for Randomised 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 9 Visit Windows After first IMP in Period B Randomised 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 - 49
V12	10	70	>49

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.

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. Baseline 2 will be the last assessment at 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 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 12 in Period B, and the Withdrawal Visit will be assigned to Visit 6 for patients withdrawn from treatment in Period A and to Visit 12 for patients withdrawn from treatment in Period B.

20.2.2 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 12 in Period B, the Withdrawal Visit for patients withdrawn from treatment in Period B will be assigned to Visit 12.

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 10, Panel 11, and Panel 12.

Panel 10 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 11 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	50-63
V12	10	70	>63

Panel 12 Visit Windows Patients Withdrawn from Treatment in Period B: PSP, NSA-4, SWN-S, Tool, MSQ, QLS, WoRQ, AIMS, BARS, mSAS

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window (days)
V6	0	0	NA
V9	4	28	day after V6-49
V12	10	70	>49

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 12 (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 and vital signs parameters 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.

If there is more than one assessment for the EPS rating scales with the maximum post-Baseline 2 value in Period B, the first value will be flagged as the maximum value.

20.3 Handling of Missing or Incomplete Dates/Times

20.3.1 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 randomised 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.

20.3.2 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.

20.3.3 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 chapter 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 12 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 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 1:st 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 12 or Withdrawal Visit: date will be imputed with latest of medication start date assuming the day is the 1:st 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 12 or Withdrawal Visit: date will be imputed with the 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 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.

20.3.4 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 20.4.2).

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 1:st of the month (e.g. if year=2017, and month=MAY, the start date would assumed 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 1:st, 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 1:st 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 1:st 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 ares 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 1:st, 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 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 a 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.

20.4 Data with Multiple Records

20.4.1 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 chapter 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.

20.4.2 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 20.3.4).

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.

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Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

Study title: Interventional, randomized, double-blind, active-controlled, fixed-dose study of Lu AF35700 in patients with Treatment-resistant Schizophrenia

SAP date: 18 October 2018

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

Authentication

Biostatistician: [redacted] Biostatistics

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Authorization

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Appendix II
Study Flow Chart

Study Procedures and Assessments

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

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

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

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

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

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

d Safety Follow-up Visit must be conducted as a visit to the clinic. The visit should be planned 6 weeks after last dose of IMP. Further Safety Follow-Up visits beyond 6 weeks may be needed as judged by the investigator (if further Safety Follow-up visits are performed, these must be recorded in the patient's medical record, and not in the eCRF). A Safety Follow-up Visit will not be performed for patients who continue in the extension study.

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

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

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

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

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

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

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

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

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

n Results will remain blinded throughout the study.

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

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

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

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

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 COUNTRY NOMWEEK2 TRT01P TRT02P USUBJID;
    model CHG =   COUNTRY NOMWEEK2 TRT01P TRT02P
              NOMWEEK2*TRT01P BASE
              NOMWEEK2*TRT02P BASE*NOMWEEK2 / ddfm = kr;
    repeated NOMINAL_WEEK / 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/standing	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/standing	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/standing	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure	OBP	mmHg	≤ -30	
Orthostatic pulse rate	OPR	beats/min		≥ 20
Temperatureb	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