Statistical Analysis Plan

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

Lu AF35700

Study No.:	16159B
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Biostatistician:	[redacted], Biostatistics
SAP date:	5 November 2019

Table of Contents

Appendices

List of Panels and Tables

List of Abbreviations and Definitions of Terms

APES	all-patients-enrolled set
APTS	all-patients-treated set
CI	confidence interval
DILI	drug-induced liver injury
eCRF	electronic case report form
EPS	extrapyramidal symptom(s)
FAS	full-analysis set
IMP	investigational medicinal product
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
PCS	potentially clinically significant
PYE	patient years of exposure
SAE	serious adverse event
SAS®	statistical software package from the SAS® Institute
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

1 Objectives

1.1 Primary Objective

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

1.2 Exploratory Objective(s)

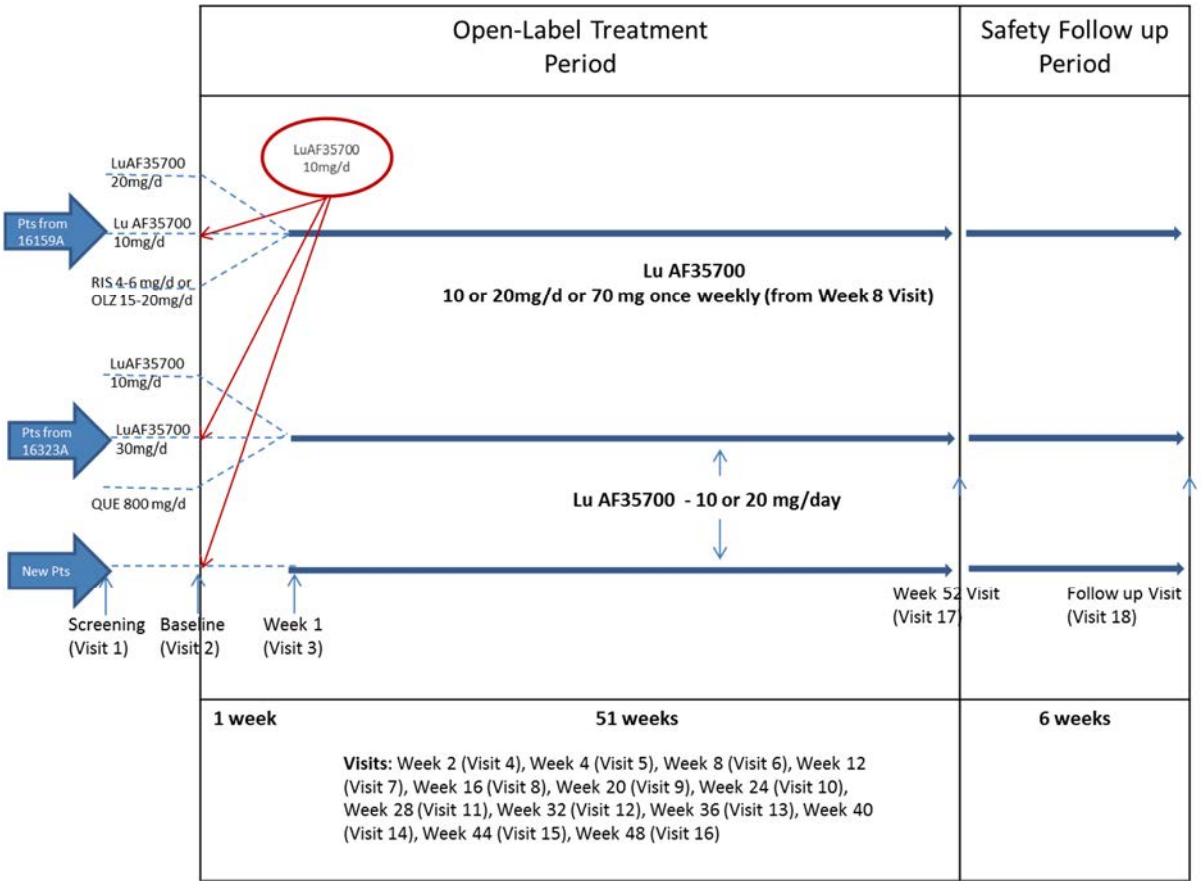
- to evaluate the long-term safety and tolerability of daily and weekly doses of Lu AF35700 in patients with schizophrenia during the 52-week treatment period
- to evaluate the therapeutic effect of daily and weekly doses of Lu AF35700 in patients with schizophrenia over a period of 52 weeks on:
  -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

2 Study Design

- This study was a multi-national, multi-site, open-label, flexible-dose, long-term (52-week) safety study in patients with schizophrenia who had participated and completed a study investigating Lu AF35700 including studies 16159A and 16323A.
- Originally, it was planned to also include patients, who had not previously participated in a study investigating Lu AF35700. However, this was never implemented due to a very high roll-over rate from study 16159A.
- The adjustment of Lu AF35700 dosing regimen (10 mg/day or 20 mg/day) during the course of the study was left to the investigator's clinical judgement.
- For patients who had completed the study 16159A, the daily dosing regimen (10 mg/day or 20 mg/day) could be switched to weekly dosing regimen (70 mg/week) according to the investigator's clinical judgement. The number of patients under weekly dosing regimen was limited to 50 patients by IVRS/IWRS.

An overview of the study is presented in Panel 1.

Panel 1 Study Design



All patients, including patients who withdraw, are scheduled for a Safety Follow-Up Visit 42 days after last dose of IMP. The follow-up includes collection of data to address the primary endpoint in a limited sense, i.e. AEs are collected if they are on-going at the Primary Outcome/Withdrawal Visit or if new SAEs have occurred. Laboratory tests are taken if these were clinically significantly abnormal at the Primary Outcome/Withdrawal Visit.

3 Definitions

3.1 Definition of Baseline

The baseline value is the value captured at the Baseline Visit of study 16159B. For efficacy/safety assessments and blood/urine samples this will be the value captured at the Primary Outcome Visit of study 16159A or at the last day of the dosing period (Day 42) in study 16323A.

For baseline characteristics captured at screening of the lead-in study, the baseline value in this study is the one captured either at the screening or baseline visit of the lead-in-study,

whichever is later. An exception to this is blood sampling for CYP2D6 and CYP2C19 genotyping, which is performed at randomization for 16159A patients.

3.2 Definition of Periods

The total study duration per patient from baseline to safety follow-up will be up to 58 weeks.

The study will consist of 2 periods:
- Treatment period – 52 weeks
- Safety follow up period – 6 weeks

3.3 Definition of Withdrawal from Treatment and Study

The group of patients who withdrew from treatment and the scheduled visits in the Treatment Period will be described as *withdrawn from treatment*. The complementary group will be described as *completed treatment*.

Patients who withdraw from treatment due to withdrawal of consent or lost to follow-up will also be described as withdrawn from study. In this case, the reason for withdrawal from study will be set to the same reason as that for withdrawal from treatment.

Patients who attend the Safety Follow-up visit (scheduled six weeks after last dose of IMP), regardless of whether they complete the Treatment period will be described as *completed study*. Patients who do not attend the Safety Follow-up visit will be described as *withdrawn from study*. This definition reflects the "Summary of Study" form in the eCRF.

4 Endpoints

Rules for calculation of derived scores and for assigning data to visits as well as descriptions of the scales used in the study are described in Section 19.

4.1 Primary Endpoints

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

4.2 Exploratory Endpoints

- Exploratory safety and tolerability endpoints:
  - Change from baseline in AIMS, BARS Global Clinical Assessment of Akathisia score (item 4) score and mSAS total score
  - C-SSRS
- Exploratory efficacy endpoints:
  - *Psychotic symptoms*
    - Change from baseline in PANSS total score
    - Change from baseline in PANSS subscale scores (PANSS Negative Symptoms subscale, PANSS Positive Symptoms subscale, PANSS General Psychopathology subscale)
  - *Negative symptoms*
    - Change from baseline in NSA-4 total score
    - Change from baseline in PANSS Marder factor score (negative symptoms)
  - *Global clinical impression*
    - Mean change from baseline in CGI-S score
  - *Andreasen symptoms remission*
    - Remission (simultaneous ratings of mild or less on PANSS specific items: P1, G9, P3, P2, G5, N1, N4, and N6) at Week 52 Visit
  - *Quality of life and functioning*
    - Change from baseline in QLS score
    - Change from baseline in TooL score
    - Change from baseline in WorQ score
    - Change from baseline in PSP total score
  - *Treatment satisfaction*
    - Change from baseline in MSQ score
  - Health care resource used during the 52-week study period

5 Analysis Sets

The patients will be assigned to analysis sets based on IMP intake and post-baseline assessments of the efficacy variable(s) in the Treatment Period.

Due to a higher-than-anticipated roll-over rate and a lower-than-anticipated attrition rate from study 16159A, only patients from study 16159A and 16323A are enrolled in the study, i.e. no patients who have not previously participated in a study investigating Lu AF35700 are enrolled.

Only 4 patients from study 16323A are enrolled. Therefore, data from these will only be presented in listings, i.e. they will not contribute to any summary tables.

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

- *all-patients-enrolled set* (APES) – all patients enrolled, including patients from study 16323A
- *all-patients-treated set* (APTS) – all patients from study 16159A who took at least one dose of Lu AF35700 in study 16159B
- *full-analysis set* (FAS) – all patients in the APTS (i.e. only patients from study 16159A are included) who had a valid baseline assessment and at least one valid post baseline assessment of PANSS total score in study 16159B.

Since this is an open-label study each patient will be classified according to these definitions based on information in data and no Classification Meeting will be held.
The classification will be done by the biostatistician.

The APTS will be used for presentations of safety data whereas the FAS will be used for presentation of efficacy data. Data listings will be based on the APES unless otherwise specified.

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.

Summaries will be prepared overall and by the previous treatment (treatment group in study 16159A). To reflect the grouping of treatments in study 16159A, these will be grouped into the following categories (for 16159A patients only):

- Lu AF35700 10 mg
- Lu AF35700 20mg
- RIS/OLZ

Unless otherwise specified, data listings will include site, previous treatment group, patient screening number (from extension study), and lead-in study-Baseline information on sex, age, race, and weight. For the data listings, the previous treatment will be displayed as the specific treatment received in the lead-in study, i.e. it will belong to one of the categories Lu AF35700 10mg, Lu AF35700 20mg, Lu AF35700 30mg, Risperidone, Olanzapine, or Quetiapine.

7 Patient Disposition

7.1 Summary of Patient Disposition

Patient disposition in the treatment period will be summarised by previous treatment group and in total, as well as by country, and will include the number of patients in each analysis set

defined in chapter 5, and the number of patients in the APTS who completed or withdrew from treatment. The number of enrolment failures will also be displayed.

7.2 Withdrawals

The number of patients who withdrew from treatment will be summarized overall and by previous treatment both by primary reason for withdrawal, and all reasons for withdrawal.

Patients who withdrew from treatment will be listed and the listing will include the reason type (primary or secondary reason for withdrawal from treatment), the reason, specification of other reason, previous treatment group, date of Visit 2, date of withdrawal from treatment, and number of days on IMP in this study. Note that patients can have more than one secondary reason for withdrawal from treatment so the listing will include both the primary reason for withdrawal from treatment and all reasons for withdrawal from treatment.

Kaplan-Meier failure plots of time to withdrawal from treatment will be presented for the total group. The time will be calculated from the date of first dose of IMP in this extension study (for handling of missing IMP start date, see section 19.3.1) to the date of completion or withdrawal from treatment. Patients who completed treatment will be regarded as censored.

All tables and graphs will be based on the APTS. Listings will be based on the APES.

8 Demographics and Baseline Characteristics

Demographics (sex, age, age group, race, and ethnicity); baseline characteristics (height, weight, BMI, and waist circumference); baseline disease characteristics (age – and years since diagnosis of schizophrenia, years since first – and number of antipsychotic treatments, number of psychiatric hospitalizations), social histories; and baseline efficacy variables (PANSS total and subscale scores, CGI-S score, and PSP total score) will be summarized overall and by previous treatment group. CGI-S will be summarized both as a continuous and a categorical variable.

Concurrent as well as relevant past medical, neurological, and psychiatric disorders at the lead-in study Screening Visit 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 of the lead-in study. A past medical, neurological, or psychiatric disorder is a disorder that ended prior to the Screening Visit of the lead-in study.

Demographics and baseline characteristics will be summarized based on the APTS, and baseline efficacy variables will be summarized based on the FAS.

9 Recent and Concomitant Medication

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

Medications will be classified according to the start and stop time and summarized by anatomical therapeutic chemical (ATC) code levels 2 and 3, generic drug name, previous treatment group, and for each of the categories:

- Medication started before first dose of IMP (i.e. on-going concomitant medication from the lead-in study) and continued after first dose of IMP
- Concomitant medication started at or after first dose of IMP

The tables will be based on the APTS.

10 Exposure and Compliance

Exposure (days) to IMP in study 16159B will be calculated as:

Last date of IMP – Start date of IMP + 1

For details about handling of missing IMP start or stop date, see section 19.3.1 (IMP Start and Stop Dates).

The exposure for patients on the weekly dosing regimen will be summarized together with the exposure for patients on the daily dosing regimens.

Exposure to IMP will be summarized overall and by previous treatment group using descriptive statistics, and summaries will include the patient years of exposure (PYE). PYE will be calculated as the sum of the number of days of exposure to IMP for each patient, divided by 365.25 days.

In addition, exposure to IMP will be categorized in intervals 1 – 84 days [0 – 3 months], 85 – 168 days [3 – 6 months], 169 – 252 days [6 – 9 months], 253 – 336 days [9 – 12 months], > 336 days [>12 months], and summarized overall and by previous treatment group.

The final dose level for patients in APTS will summarized overall and by previous treatment group.

The number of patients switching to the weekly dosing regimen will be summarized based on the APTS. The summary will include the number of patients going back to daily dosing after initiating weekly dosing.

Non-compliant days are days 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 (%) with IMP for the Treatment Period will be calculated as:

$$\frac{\text{Last date of IMP} - \text{Start date of IMP} + 1 - \text{Number of non-compliant days}}{\text{Last date of IMP} - \text{Start date of IMP} + 1} \times 100$$

where the number of non-compliant days is defined as the sum of all non-compliant days from the start of the interval to the end of the interval.

The compliance for patients on the weekly dosing regimen will be summarized together with the compliance for patients on the daily dosing regimens.

Compliance with IMP will be categorized as "≤80% compliant" or ">80% compliant". The number and percentage of patients in each category will be summarised by previous treatment group and in total based on the APTS.

Exposure and compliance will be summarized based on the APTS.

11 Efficacy

11.1 General Efficacy Analysis Methodology

Unless otherwise specified, all the efficacy analyses will be based on the FAS.

All the tables and graphs will be presented overall and by previous treatment group unless otherwise specified.

All the confidence intervals (CIs) will be two-sided, 95% CIs.

Descriptive statistics for the absolute scores and the change from baseline scores for the efficacy variables will be presented by study week using all available observations (observed cases [OC] data). The tables will be repeated for LOCF values.

11.2 Exploratory Analysis of Efficacy

Changes from baseline in PANSS total score, PANSS subscale scores (PANSS Negative Symptoms subscale, PANSS Positive Symptoms subscale, PANSS General Psychopathology subscale, and PANSS Marder factors), NSA-4 total score, CGI-S score, QLS score, TooL score, WorQ score, PSP total score, and MSQ score will be analysed using a restricted maximum likelihood (REML)-based Mixed Models for Repeated Measurements (MMRM) approach. The analysis will be based on the FAS.

The model will include the following fixed effects: country and week as factors, baseline score as a continuous covariate, and baseline score-by-week interaction. An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The estimated mean changes from baseline will be reported with two-sided 95% confidence intervals.

The estimated mean change from baseline in PANSS total score by visit week will be plotted for the total group.

The SAS code for fitting the MMRM models is shown in Appendix II.

For PANSS total score, PANSS Negative Symptoms subscale score, PANSS Positive Symptoms subscale score, PANSS Negative Symptoms Marder factor score, a further exploratory analysis will be presented where previous treatment and previous-treatment-by-week interaction are added as fixed effects to the model described above. For these analyses, the estimates from the MMRM analysis will be presented by previous treatment.

Tables displaying the counts and proportion of patients in remission according to the Andreasen symptoms remission criteria described in section 19.1.2 (simultaneous ratings of mild or less on items P1, G9, P3, P2, G5, N1, N4, and N6, see Panel 4 and Panel 5) will be presented both by previous treatment and for the total group, for LOCF values only.

HEA items will be summarized overall and by previous treatment group for the Baseline Visit and the Primary Outcome/Withdrawal Visit based on the APTS.

12 Safety

12.1 Adverse Events

12.1.1 General Methodology for Adverse Events

Unless otherwise specified, tables, and graphs will be based on the APTS. Listings will be based on the APES.

All the tables will be presented for the total group. Three tables will be split by previous treatment as well, see section 12.1.6 and 12.1.9.

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

Only stop-dates for ongoing events at the Primary Outcome/Withdrawal Visit, and new SAEs are collected in the Follow-up Period. Therefore, adverse events in the Follow-up Period will be included in the summaries for the Treatment Period (periods are defined in section 12.1.3).

Listings of adverse events will be sorted by site, previous treatment group, patient screening number (from the extension study), and adverse event start date, and include preferred term, investigator term, adverse event start date, days since first dose of IMP, 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 dates (see section 19.3.5) will be included in the listings, where information about the imputation will be included as a flag in the end of the date (M = month and day imputed or D = day imputed).

12.1.2 Classification of Adverse Events

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

- *pre-study adverse event* – an adverse event that starts before the date of first dose of IMP in study 16159B.
- *treatment-emergent adverse event* (TEAE) – an adverse event that starts, increases in intensity compared to the preceding intensity, or changes from non-serious to serious on or after the date of first dose of IMP in study 16159B.

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

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

12.1.3 Coding of Adverse Events

Adverse events will be coded using MedDRA, Version 22.0 or later.

12.1.4 Allocation of AEs to Treatment Periods

AEs will be allocated to treatment periods according to the time of onset of the adverse event (for handling of incomplete start dates, see section 19.3.5):

- *AE in Lead-in Study Period* – an AE that starts before first dose of IMP in study 16159B
- *AE in the Treatment Period* – an AE that starts at or after the date of first dose of IMP in study 16159B and at or before the date of the Primary Outcome/Withdrawal Visit
- *AE in the Safety Follow-up Period*– an AE that starts after the last visit in the Treatment Period

12.1.5 Presentation of Adverse Events

All adverse events will be listed for the APES, including a flag for TEAEs.
A listing of all AEs occurring while on weekly dosing will also be presented.

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

12.1.6 Presentation of Treatment-emergent Adverse Events

The following summaries will be provided for the APTS:

- TEAEs by SOC and preferred term
- TEAEs by preferred term – both by previous treatment and overall
- TEAEs occurring while on weekly dosing by preferred term
- TEAEs by sex and preferred term
- causally related TEAEs by SOC and preferred term
- TEAEs by intensity (*mild*/*moderate*/*severe*) and preferred term
- causally related TEAEs by intensity and preferred term
- TEAEs within the first 2 weeks of study 16159B by preferred term – both by previous treatment and overall

12.1.7 Presentation of Deaths

All adverse events for patients who died will be listed.

12.1.8 Presentation of Serious Adverse Events

All SAEs will be listed.

Treatment-emergent SAEs for the APTS will be summarized by:

- SOC and preferred term
- preferred term

Treatment-emergent SAEs for the APTS occurring while on weekly dosing will also be summarized by preferred term.

12.1.9 Presentation of Adverse Events Leading to Withdrawal

All adverse events leading to withdrawal will be listed.

TEAEs leading to withdrawal for the APTS will be summarized by:

- SOC and preferred term
- preferred term and previous treatment

Treatment-emergent AEs leading to the withdrawal occurring while on weekly dosing will also be summarized by preferred term for the APTS.

12.1.10 Adverse Events Leading to Dose Reduction

Adverse events leading to reduction of dose of Lu AF35700 in the Treatment Period will be listed.

Adverse events leading to reduction of dose of Lu AF35700 in the Treatment Period will be summarized by preferred term.

12.2 General Methodology for Other Safety Data

For details about data handling, see sections 19.1 and 19.2.

Unless otherwise specified, tables and graphs will be based on the APTS, and listings will be based on the APES.

All the tables and graphs will be presented for the total group.

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

Descriptive statistics for the safety variables, both absolute values and changes from baseline, will be presented by visit and for the last assessment. All available post-baseline assessments will be included in the identification of the last assessment except for assessments made at the safety-follow-up visit.

The number and percentage of patients with at least one PCS value at any post-baseline assessment time point will be summarized by variable. All available assessments will be included in the evaluation of PCS values except for assessments made at the safety-follow-up visit.

For patients with post-baseline 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 the adverse events in patients with post-baseline PCS values will be listed by previous treatment group and patient screening number (from the extension study); the listings will include all available values for the variable with flagging of PCS values and out-of-reference-range values, the assessment date, the change from baseline in PCS value, the preferred term for the adverse event, and start date, 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.

12.3 Clinical Safety Laboratory Test Data

12.3.1 Data Presentation

The PCS criteria used for the clinical safety laboratory tests are the Lundbeck standard PCS criteria described in SOP_09978: *PV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 1.

The clinical safety laboratory test values will be presented either in conventional or Système International (SI) units.

Descriptive statistics for the laboratory parameters in the Treatment Period, both absolute values and changes from baseline, will be presented by test and week and the last assessment in the Treatment Period. The summaries for the absolute values will also include summaries for baseline.

The number and percentage of patients with at least one PCS low value or PCS high value at any post-baseline assessment in the Treatment Period will be summarized by laboratory parameter. 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 detailed previous treatment group, i.e. where the RIS/OLZ group is split into whether the patient received Risperidone or Olanzapine in the lead-in study as well as by sex.

12.3.2 Potential Drug-induced Liver Injury (DILI)

Signals of DILI will be assessed according to the FDA guideline[1] using the following criteria:

- alanine or aspartate 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

Patients fulfilling any of the criteria (ALT/AST, ALP, or BILI) will be listed, and the listing will include all available ALT, AST, BILI, and ALP, BILI, EOSLE (Eosinophils (% of total leukocytes)), and GGT (gamma glutamyl transferase) values (absolute and normalised) sorted by assessment date in ascending order.

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
- alkaline phosphatase <2×ULN AND
- total bilirubin >2×ULN

In the summaries, each patient should be counted only once using the maximum assessment, or the most severe for the combined criteria. The summaries will also include number of potential Hy's Law cases.

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 the Treatment Period. The criteria for the individual tests will be considered separately (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 the Treatment Period. The test values will be normalised by the ULN (unit xULN) and the Y-axis will be on the log scale. All assessments at baseline or later will be included, and the time will be days since first IMP in the extension study. Reference lines for the day of first and last date of IMP (in the extension study) will be included. If there is more than one assessment at the same time point for a test, the maximum value will be used.

12.4 Vital Signs and Weight

The PCS criteria used for vital signs and weight are the Lundbeck standard PCS criteria described in SOP_09978: *PV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 2.

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

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

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

12.5 ECGs

The PCS criteria used for the ECG parameters are the Lundbeck standard PCS criteria described in SOP_09978: *PV – PCS and standard reference values for laboratory investigations, vital signs and ECGs in clinical studies*, version 6, and are also included in Table 3.

Descriptive statistics for the ECG parameters in the Treatment Period, both absolute values and changes from baseline, will be presented by test and week and the last assessment in the

Treatment Period. The summaries for the absolute values will also include summaries for baseline.

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

12.6 Other Safety Endpoints(s)

12.6.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Scores

Since no patients who had not previously participated in a study investigating Lu AF35700 were enrolled in study 16159B, only the *Since Last Visit Version* of the C-SSRS will be considered.

The C-SSRS was administered:

- at baseline (using the *Since Last Visit Version*) – the C-SSRS assessment at baseline that collects information since the previous visit. For 16159A patients this is the assessment performed at the Primary Outcome Visit of study 16159A and for 16323A patients this is the assessment performed at the last day of the dosing period in study 16323A.
- post-baseline (using the *Since Last Visit Version*) – the C-SSRS assessments after baseline

The C-SSRS scores post-baseline will be summarized based on the APTS. For the post-baseline assessments the score will be derived as the most severe item that the patient answered "Yes" to during the entire Treatment Period.

The definition of "most severe" is given by the ordering in Panel 2.

The number and percentage of patients with *no suicidal ideation or behaviour* will be included in the summaries. Patients in this category are those who:

- answered 'no' to all ideation and behaviour questions; that is, answered 'no' to items 1 to 5 in Panel 2 (related to suicidal ideation) and answered 'no' to items 6 to 10 in Panel 2 (related to suicidal behaviour)

For the summary of the post-baseline scores, these patients will be the ones that at all assessments during the Treatment Period fulfilled this criterion.

Panel 2 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)	

Missing C-SSRS scores will not be imputed.

Non-suicidal self-injurious behaviour is considered separately. For the post-baseline assessments it will be identified whether the patient had *non-suicidal self-injurious behaviour* (patient answered 'Yes' to the item at any of the visit(s) in the Treatment Period). The number and percentage of patients with *non-suicidal self-injurious behaviour* will be included in the summaries.

For patients with any post-baseline suicidal behaviour (C-SSRS scores of 6 to 10), listings will be provided including all C-SSRS scores for those patients; C-SSRS scores related to suicidal behaviour will be flagged.

12.6.2 EPS Rating Scale Scores

For details about data handling, see section 19.1, 19.2.

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

The single-item scores for AIMS items 8 to 12 and BARS items 1 to 4 will be summarized by visit.

13 Pharmacokinetic/Pharmacodynamic Analyses

No pharmacokinetic/pharmacodynamics analyses are planned.

14 Blinded Data Reviews

Not applicable.

15 Interim Analyses

Not applicable.

16 Sample Size Considerations

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

As stated in the clinical study protocol, it was expected that approximately 400 patients would be enrolled in the study distributed as follows: 270 from study 16159A, 30 from study 16323A and 100 patients who had not previously participated in a study investigating Lu AF35700. However, the distribution of the number of patients could be adjusted based upon the recruitment rate in each group. As mentioned in section 2, the actual patients recruited were for the most part from study 16159A except for 4 patients from study 16323A.

Since more than 500 patients are included in the study, it will be possible to obtain solid information on long-term safety of Lu AF35700.

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

17 Statistical Software

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

18 Changes to Analyses Specified in the Protocol

Due to the results from the lead-in study 16159A from which the majority of patients come from, the following changes have been made:

As mentioned in section 2, due to a higher-than-anticipated roll-over rate and a lower-than-anticipated attrition rate from study 16159A, only patients from study 16159A and 16323A are enrolled in the study and the majority of the patients enrolled are from study 16159A.

The 4 patients enrolled from study 16323A come from different treatment regimens than those from study 16159A. Therefore, data from these 4 patients will only be presented in listings, i.e. they will not contribute to any summary tables.
This also means that the definition of the previous treatment groups included in this document have been changed from what was defined in the study protocol to accurately reflect the treatment received in the lead-in study.
Another implication of this change is that the analysis sets defined in section 5 have been updated to facilitate the analyses as well as to make it possible to include the patients from 16323A in listings.

The clinical study protocol defines the baseline just prior to randomization in study 16159A as an additional baseline and specifies that summary tables will be prepared both with respect to that baseline and the baseline defined in this document. However, these additional summaries will not be created, as it is considered sufficient to evaluate the data captured in this long-term study alone.

The above change also means that the baseline term referring to baseline just prior to randomization in study 16159A is removed from all statistical models.

In the protocol, it is stated that separate displays of descriptive statistics will be prepared for patients only receiving daily dosing in study 16159B. This will not be done, as it is considered sufficient to provide the tables including all patients regardless of dosing regimen.

19 Details on Data Handling

19.1 Derived Variables

19.1.1 Missing Items

If >20% of the items for a rating scale or subscale are missing, the total score or subscore will be set to missing. For the NSA-4 rating scale, however, the total score will be set to missing, if any of the individual items are missing, see also section 19.1.5. The implications of these rules are summarized in Panel 3. If ≤20% of the items is missing and imputation should be done, the missing items will be imputed with the mean of the recorded items.

Panel 3 Maximum Number of Missing Items on Rating Scales

PARAMCD	Description	Maximum Number of Missing Items
PANSSTOT	PANSS total score	6
POSITOT	PANSS Positive Symptom subscale score	1
NEGATOT	PANSS Negative Symptom subscale score	1
GENTOT	PANSS General Psychopathology subscale score	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
ANREMIS	PANSS Andreasen Symptoms remission score	0
NSATOT	NSA-4 total score	0
QLSTOT	QLS total score	4
WORQTOT	WoRQ total score	1
TOOLTOT	TooL total score	1
MSASTOT	Modified Simpson-Angus Scale (mSAS) total score	2
AIMSTOT	Abnormal Involuntary Movement Scale (AIMS) total score	1

19.1.2 PANSS

The PANSS[2] 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 Symptoms subscale, Negative Symptoms subscale, and General Psychopathology subscale. Furthermore, the division of PANSS into the 5 PANSS Marder factors[3] is used. The five factors are: Negative symptoms, Positive Symptoms, Disorganized Thought, Uncontrolled Hostility/Excitement, and Anxiety/Depression. The binary Andreasen score of remission will also be derived from the PANSS scores. If any of the items used in the derivation of the remission score are missing, the derived score is also set to missing.

The PANSS items and the derivation of the total score, the subscale scores, the factor scores, and the remission scores are described in Panel 4 and Panel 5.

Panel 4 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
Stereotyped thinking	PANSS14	Preoccupation	PANSS29
		Active social avoidance	PANSS30

Panel 5 Derivation of PANSS Total Score and Subscales

PANSS Total Score and Subscales	Derivation
PANSS Total Score	Sum of all items PANSS01 to PANSS30
PANSS Positive Symptoms subscale score	Sum of items PANSS01 to PANSS07
PANSS Negative Symptoms subscale score	Sum of items PANSS08 to PANSS14
PANSS General Psychopathology subscale score	Sum of items PANSS15 to PANSS30
PANSS Negative Symptoms factor score	Sum of items PANSS08 to PANSS11, PANSS13, PANSS21, and PANSS30
PANSS Positive Symptoms factor score	Sum of items PANSS01, PANSS03, PANSS05, PANSS06, PANSS14, PANSS15, PANSS23, and PANSS26
PANSS Disorganized Thought factor score	Sum of items PANSS02, PANSS12, PANSS19, PANSS24, PANSS25, PANSS27, and PANSS29
PANSS Uncontrolled Hostility/Excitement factor score	Sum of items PANSS04, PANSS07, PANSS22, and PANSS28
PANSS Anxiety/Depression factor score	Sum of items PANSS16 to PANSS18, and PANSS20
PANSS Andreasen Symptoms remission score	If PANSS01, PANSS02, PANSS03, PANSS08, PANSS11, PANSS13, PANSS19, PANSS23 ≤ 3 then it equals 'Yes' otherwise it equals 'No'

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

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

CGI-S rates the severity of the patient's current mental illness on a 7-point scale ranging from 1 (normal – not at all ill) to 7 (among the most extremely ill patients).

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

19.1.4 Personal and Social Performance Scale (PSP)

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

The PSP scale consists of a 100-point single-item rating scale, subdivided into 10 equal intervals. Scores of 1 to 10 indicate lack of autonomy in basic functioning, whereas scores of 91 to 100 reflect excellent functioning. The 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.

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.

19.1.5 4-Item Negative Symptom Assessment (NSA-4)

The NSA-4[6] 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' for the 4 items. The overall global rating of negative symptoms is rated on a 1 to 7-point scale where '1' represents no evidence of the symptoms and '7' represents extremely severe symptoms.

The NSA-4 Total Score is the sum of all 4 items and the global rating and thus ranges from 5 to 31. Since the global rating has a different range than the 4 items, the total score is only calculated if no items are missing. When calculating the total score, items rated as '9' (non-ratable) are treated as missing. This implies that if a patient has a score of '9' in any of the 4 items, the total score is also set to "missing", following the specification given in Panel 3.

19.1.6 Quality of Life Scale (QLS)

The QLS[7] is a clinician-rated scale designed to assess deficit symptoms of schizophrenia and functioning during the preceding 4 weeks. The QLS consists of 21 items in 4 subscales:

Interpersonal Relations (8 items), Instrumental Role (4 items), Intrapsychic Foundations (7 items), and Common Objects and Activities (2 items). Each item is rated on a 7-point scale, from 0 (severe impairment) to 6 (normal or unimpaired functioning). Definitions are provided for 4 anchor points of the 7 points.

The total score is the sum of all 21 items and ranges from 0 to 126.

Note, if item 1 is rated 9, 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 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 3).

19.1.7 Readiness for work questionnaire (WoRQ)

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

The total score will be derived as the sum of items 1-7.

19.1.8 Medication Satisfaction Questionnaire (MSQ)

The MSQ[9] 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).

19.1.9 Tolerability and Quality of Life questionnaire (TooL)

The TooL[10] 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 are derived as the sum of the single items and range from 8 (no impact) to 32 (maximum impact).

19.1.10 Abnormal Involuntary Movement Scale (AIMS)

The AIMS[11] 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.

19.1.11 Barnes Akathisia Scale (BARS)

The BARS[12] is a clinician-rated scale designed to assess the presence and severity of drug induced akathisia. The BARS consists of 4 items: one objective item (observed restlessness), two subjective items (patient's awareness of restlessness and related distress), and a global clinical assessment of akathisia. The objective and subjective symptoms are rated on a 4-point scale, from 0 (no symptom) to 3 (severe symptoms). The global clinical assessment is rated on a 6-point scale from 0 (absent) to 5 (severe akathisia).

In the analyses, the global clinical assessment (item 4) will be used.

19.1.12 Modified Simpson Angus Scale (mSAS)

The SAS[13] is a clinician-rated scale designed to assess the presence and severity of drug-induced parkinsonism. The mSAS consists of 10 items to evaluate gait, rigidity (arms and head), eye-blinking, tremor, salivation and akathisia. The 10 items are assessed using a neurological examination and rated on a 5-point scale, from 0 (absence of the condition) to 4 (most extreme form of the condition). Comprehensive definitions are provided for each anchor point on the scale.

The mSAS Total Score is the sum of all 10 items and ranges from 0 to 40.

19.1.13 Health Care Resource Utilisation (HEA)

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

19.2 Assigning Data to Visits

19.2.1 Rating Scales

The assessment at the Withdrawal Visit for patients withdrawn from treatment will be assigned to a nominal visit in the Treatment Period, according to the visit windowing specified in Panel 6 and Panel 7.

In analyses of efficacy, if the Withdrawal Visit is assigned to the same visit as a scheduled visit, the assessment from the Withdrawal Visit, which by definition always will be the latest, will be used.

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

Otherwise, the assessments at the scheduled visits will be used.

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

Panel 6 Visit Windows: PANSS, CGI-S, C-SSRS

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V2 (Baseline Visit)	0	0	NA
V3	1	7	Day after V2 – 11
V4	2	14	12-21
V5	4	28	22-42
V6	8	56	43-70
V7	12	84	71-98
V8	16	112	99-126
V9	20	140	127-154
V10	24	168	155-182
V11	28	196	183-210
V12	32	224	211-238
V13	36	252	239-266
V14	40	280	267-294
V15	44	308	295-322
V16	48	336	323-350
V17 (Primary Outcome/Withdrawal Visit)	52	364	>350

Panel 7 Visit Windows: PSP, NSA-4, QLS, WoRQ, TooL, MSQ, AIMS, BARS, mSAS

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V2 (Baseline Visit)	0	0	NA
V5	4	28	14-42
V10	24	168	154-182
V17 (Primary Outcome/Withdrawal Visit)	52	364	>350

For efficacy assessments, the last usable assessment in the Treatment Period will be used to impute missing values for the LOCF. For patients that have a missing visit, the value from the

visit before will be used for imputing the missing value for the LOCF. If the missing visit is the one directly following the baseline visit, however, the value will not be imputed for the LOCF, as baseline observations will not be carried forward.

The Health Economics Assessment (HEA) scale is only scheduled to be assessed at Visit 17. For these assessments, the Withdrawal Visit for patients withdrawn from treatment in the Treatment Period will be assigned to Visit 17.

19.2.2 Safety Variables

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, Panel 9 and Panel 10. Note, assessments after Visit 2 for enrolled patients that did not have any IMP intake will be assigned to nominal Visit 2.

In analyses of vital signs parameters using visit, if the Withdrawal Visit is assigned to the same visit as a scheduled visit, the assessment at the Scheduled Visit will be used.

For 16159A-patients, additional ECG assessments will be performed if the daily dosing is switched to weekly dosing. These assessments will not be windowed.

Panel 8 Visit Windows: Vital Signs

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V2 (Baseline Visit)	0	0	NA
V3	1	7	Day after first IMP – 11
V4	2	14	12-21
V5	4	28	22-35
V6	8	56	49-63
V7	12	84	77-91
V8	16	112	105-119
V9	20	140	133-147
V10	24	168	161-175
V11	28	196	189-203
V12	32	224	217-231
V13	36	252	245-259
V14	40	280	273-287
V15	44	308	301-315
V16	48	336	329-343
V17 (Primary Outcome/Withdrawal Visit)	52	364	>357

Panel 9 Visit Windows: Laboratory Tests, Body weight, and Waist circumference

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V2 (Baseline Visit)	0	0	NA
V5	4	28	22-35
V10	24	168	161-175
V17 (Primary Outcome/Withdrawal Visit)	52	364	>357

Panel 10 Visit Windows: ECG

Nominal Visit Number	Nominal Visit Week	Nominal Visit Day	Time Window
V2 (Baseline Visit)	0	0	NA
V5	4	28	22-35
V8	16	112	105-119
V11	28	196	189-203
V14	40	280	273-287
V17 (Primary Outcome/Withdrawal Visit)	52	364	>357

Note that if the first IMP in the Treatment Period 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.

The Baseline value 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 last post-baseline assessments in the Treatment Period, 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 assessments 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.

19.3 Handling Missing or Incomplete Dates/Times

19.3.1 IMP Start and Stop Dates

A missing IMP start date will be imputed with the date of Visit 2.

A missing IMP stop date will not be imputed.

Exposure and compliance will not be calculated for patients with missing IMP start-or-stop dates. Thus, a patient with a missing IMP start-or-stop date will contribute as having no exposure in the calculation of PYE. This also holds for patients not receiving any IMP.

19.3.2 Withdrawal Date

Missing withdrawal dates will not be imputed and time to withdrawal from treatment will not be calculated for missing withdrawal dates.

19.3.3 Medical Disorder Start and Stop Dates

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

19.3.4 Medication Start and Stop Dates

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

In general, if the medication *start* date is partially or completely missing and if the medication is on-going from the lead-in study, the start date will be imputed with the imputation value used in the lead-in study.

Otherwise, the following rules will be applied:

- *Incomplete start date where day is missing:*
  - The start date will be imputed with the latest of either the date of first IMP in the extension study or the medication start date assuming that the day is the 1st of the month.
- *Incomplete start date where month and day are missing:*
  - If the year is equal to the year of first IMP in the extension study the date will be imputed with the date of first IMP in the extension study.
  - If the year is after the year of first IMP in the extension study the date will be imputed with the medication start date assuming the month and day are January 1st.
- *Missing start date:*
  - The medication start date will be imputed with the date of first IMP in the extension study
- *Incomplete end date where day is missing:*
  - The date will be imputed with the minimum value of either the last day of the reported month and year or the end of study date.
- *Incomplete end date where month and day are missing:*
  - The date will be imputed with the minimum value of either December 31st of the reported year or the end of study date.
- *Missing end date:*
  - If the medication end date is missing and the medication is not reported as on-going, the end date will be imputed with the end of study date.

19.3.5 Adverse Event Start and Stop Dates

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

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

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

In general, if the AE is on-going at Baseline and the start date is partially or completely missing, the start date will be imputed with the imputation value used in the lead-in study.

- Patients not in APTS:
  - *Incomplete start date where day is missing*
    The start date will be imputed with the latest of adverse event start date

assuming the day is the 1st of the month (e.g. if year=2017, and month=MAY, the start date would assumed to be 01MAY2017), and date of Visit 2

- *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 1st, and date of Visit 2

- 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 the Treatment Period, the date will be imputed with the latest of adverse event start date assuming the day is the 1st of the month, and Visit 2
    - If the start year and month are at or after the year and month of first IMP in the Treatment Period and at or before the last visit in the Treatment Period, the date will be imputed with the latest of adverse event start date assuming the day is the 1st of the month, and the date of first IMP in study 16159B
    - If the start year and month are after the year and month of the last visit in the Treatment Period, the date will be imputed with the latest of adverse event start date assuming the day is the 1st of the month, and the day after last visit in the Treatment Period
  - *Incomplete start date where month and day are missing*
    - 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 1st, and date of Visit 2
    - If the year is equal to the year of first IMP in the Treatment Period, the date will be imputed with the date of first IMP in study 16159B

For adverse events with incomplete end dates 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 imputed with the minimum of the 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 dates 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 the Treatment Period was 17MAY2017, and the incomplete date for change in intensity was 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 the Treatment Period was 02MAY2017, and the incomplete date for change in intensity was 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 the Treatment Period was 13APR2017, and the incomplete date for change in intensity was 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 later intensity change, 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 comes after.

The imputed start dates will be used in the classification of adverse events as TEAEs (see section 12.1.2). TEAEs will be flagged in the data.

19.4 Data with Multiple Records

19.4.1 Dose Changes in Medication

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.

19.4.2 Changes in Intensity or Seriousness of Adverse Events

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

If the recorded start date of a serious adverse event is after the start date of the reported adverse event, the event is considered as having changed from non-serious to serious.

Recorded seriousness for an adverse event will be the most serious (mapped to SDTM variable AESER, i.e. AESER=Y for an adverse event that change from non-serious to

serious). In ADaM data, one additional row will be added for an adverse event that change from non-serious to serious, one with seriousness non-serious and one with seriousness serious (ADaM variable ASER). The stop date for the first row (ASER=N) will be the start date of the serious adverse event minus 1, and the stop date for the second row (ASER=Y) will be the stop date for the adverse event. After having 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, one for each change type. This is to keep the transparency and to keep the value of the SDTM variable FASTRESC, which is mapped to the ADaM dataset. To be able to summarize the number of adverse events without counting these events twice, a flag will be added to the data indicating which adverse events that will go into the summaries.
As an example, an adverse event originally reported as being mild and non-serious, which additionally is reported as having changed to severe and serious on the same date, will have a total of 3 rows in data. One row with intensity mild, seriousness non-serious, and ANL01FL = 'Y', one row with intensity severe, seriousness non-serious, and ANL01FL = '' (empty), and one row with intensity severe, seriousness serious, and ANL01FL = 'Y'.

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 a single event in the summaries.

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

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

References

1. United States Food and Drug Administration (US FDA). Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009.
2 . Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987; 13(2): 261-276.
3. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry. 1997; 58(12):538-546.
4. Guy W, editor. Clinical Global Impressions. In: Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. Revised ed. Rockville, MD: National Institute of Mental Health; 1976; 217-222.
5. Morosini P-L, Magliano L, Brambilla L et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. Acta Psychiatrica Scandinavica 2000; 101: 323-9
6. Alphs L, Morlock R, Coon C, van Willigenburg A, Panagides J. The 4-item negative symptom assessment (NSA-4) instrument: A simple tool for evaluating negative symptoms in schizophrenia following brief training. Psychiatry. 2010; 7: 26-32.
7 . Heinrichs DW, Hanlon TE, Carpenter WT. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull. 1984; 10: 388-398.
8 . Potkin SG, Bugarski-Kirola D, Edgar CJ, Soliman S, Le Scouiller S, Kunovac J et al. Psychometric evaluation of the Work Readiness Questionnaire in schizophrenia. CNS Spectr. 2014; Oct 1: 1–8.
9 . Vernon MK, Revicki DA, Awad AG, Dirani R, Panish J, Canuso CM et al. Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. Schizophr Res. 2010; 118(1-3): 271-278.
10 . Lindström E, Jönsson L, Berntsson A. A patient perspective on side effects of antipsychotic therapy: the TooL instrument. Value Health. 2009; 12: A361.
11. Guy W editor. ECDEU Assessment Manual for Psychopharmacology. Revised ed. Rockville, MD: National Institute of Mental Health; 1976:534-6
12. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry.1989;154:672-6
13. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970;212:11-9

Appendix I
Statistical Analysis Plan
Authentication and Authorization

Statistical Analysis Plan
Authentication and Authorization

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

Study No.: 16159B

SAP date: 5 November 2019

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

Authentication

Biostatistician: [redacted]

Clinical research scientist: [redacted]

Authorization

Head of Biostatistics: [redacted]

Appendix II

SAS® Code

SAS® Code

The code for fitting the overall models mentioned in section 11.2 is given below.
The variable CHG refers to the change from baseline value, NOMWEEK refers to the week variable, COUNTRY to the country variable, USUBJID to the subject identifier variable, and BASE refers to the baseline value.

```
proc mixed data = xxx order = internal method = reml;
        class COUNTRY NOMWEEK USUBJID;
        model CHG = COUNTRY NOMWEEK BASE BASE * NOMWEEK / ddfm = kr;
        repeated NOMWEEK / subject = USUBJID type = un;
        lsmeans NOMWEEK / cl alpha = 0.05;
quit;
```

Appendix III
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)	≥ 16.5 (women)
			≤ 11.5 (men)	≥ 18.5 (men)
B-erythrocytes (red cell count)	RBC	x 10E12/L	≤ 3.5 (women)	≥ 6.0 (women)
			≤ 3.8 (men)	≥ 7.0 (men)
B-haematocrit (packed cell volume)	HCT	V/V	≤ 0.32 (women)	≥ 0.50 (women)
			≤ 0.37 (men)	≥ 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

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
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
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

Laboratory Test	CDISC Term	Unit	PCS Low	PCS High
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

Variable	CDISC Term	Unit	PCS Low	PCS High
Waist circumference	WSTCIR	Cm	decrease ≥ 7%	increase ≥ 7%
Weight	WEIGHT	Kg	decrease ≥ 7%	increase ≥ 7%
Body Mass Index	BMI	kg/m2	decrease ≥ 7%	increase ≥ 7%
Pulse rate, supine/sitting/unknown	PULSE	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
Diastolic blood pressure, supine/sitting/unknown	DIABP	mmHg	≤ 50 and decrease ≥ 15	≥ 105 and increase ≥ 15
Systolic blood pressure, supine/sitting/unknown	SYSBP	mmHg	≤ 90 and decrease ≥ 20	≥ 180 and increase ≥ 20
Orthostatic systolic blood pressure	OBP	mmHg	≤ -30	
Orthostatic pulse rate	OPR	beats/min		≥ 20
Temperature	TEMP	ºC	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	PRMEAN	Msec		≥ 260
QRS interval	QRSDUR	Msec		≥ 150
QT interval	QTMEAN	Msec		≥ 500
Derived Time Interval				
Heart rate	HRMEAN	beats/min	< 50 and decrease ≥ 15	≥ 120 and increase ≥ 15
QTcB interval	QTCB	Msec	< 300	> 500 or increase > 60
QTcF interval	QTCF	Msec	< 300	> 500 or increase > 60

Increase/decrease is relative to the baseline value.

Appendix IV
Study Flow Chart

Study Flow Chart

Study Procedures and Assessments

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

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

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

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

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

d. The Safety Follow-up Visit will be done 6 weeks (+3 days) after the last dose of IMP. This visit can be a telephone contact, unless an SAE has occurred since last visit or unless there was a clinically

significant abnormal safety laboratory test value at the last visit. In such cases, safety follow-up(s) must be scheduled to allow for a medical examination and/or blood sampling. Further Safety Follow-up Visits beyond 6 weeks may be needed as judged by the investigator (if further Safety Follow-up Visits are performed, these must be recorded in the patient's medical record, and not in the CRF).

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