A Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Risperidone Extended Release Capsules in Subjects with Schizophrenia, Schizoaffective Disorder

Statistical Analysis Plan

VERSION: FINAL 1.0
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21-Oct-2020

STUDY DRUG / PROTOCOL ID:
Risperidone extended release capsule / LYN-005-C-004

PREPARED FOR:

Lyndra Therapeutics, Inc. (US)

Sponsor: Lyndra Therapeutics, Inc. (US)
Protocol Number: LYN-005-C-004
SAP Version and Date: Final 1.0, 21OCT2020

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Sponsor: Lyndra Therapeutics, Inc. (US)
Protocol Number: LYN-005-C-004
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Contents

ABBREVIATIONS

AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
AUC	Area Under the Concentration vs Time Curve
C_{max}	Maximal Observed Concentration
CGI-S	Clinical Global Impression of Severity
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DIMD	Drug-Induced Movement Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EPS	Extrapyramidal Symptoms
ER	Extended Release
ESRS	Extrapyramidal Symptom Rating Scale
GI	Gastrointestinal
IRT	Interactive Response Technology
Kel	First Order Elimination Rate Constant
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Medical Activities
PANSS	Positive and Negative Syndrome Scale
PI	Principal Investigator
PK	Pharmacokinetics
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
SAE	Serious adverse events
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
T_{max}	Time to Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Event
ULN	Upper limit of normal

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1 INTRODUCTION

The statistical analysis plan (SAP) details the planned analysis required to satisfy the Clinical Study Report (CSR) of study number LYN-005-C-004: A Multiple Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of Risperidone Extended Release Capsules in Subjects with Schizophrenia, Schizoaffective Disorder. The content of this SAP is based on the protocol dated 29AUG2020 V2.0.

Revision Chronology:

1.0	16OCT2020	Original

Mock shells for tables, listings, and figures will be included in a separate document.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To determine the safety and tolerability of risperidone extended release capsules (LYN-005) administered as repeat weekly doses compared to IR risperidone tablets at 2 dose levels;
- To characterize the PK of risperidone, active metabolite 9-hydroxyrisperidone and active moiety risperidone and 9-hydroxyrisperidone combined) after repeat weekly doses of LYN-005 ER capsules relative to IR risperidone tablets at 2 dose levels.

2.1.2 Secondary Objectives

- To assess the exposure to risperidone, 9-hydroxyrisperidone and active moiety during the switch from IR risperidone to LYN-005.

2.1.3 Exploratory Objectives

- To model the PK of risperidone, 9-hydroxyrisperidone and active moiety when administered as a LYN-005 extended-release capsule.

2.2 Study Endpoints

2.2.1 Primary Endpoints

- Incidence of treatment emergent adverse events (TEAEs).
- Risperidone, 9-hydroxyrisperidone, and active moiety PK after oral administration of LYN-005 capsules and IR risperidone to include, as possible and appropriate, C_{max}, C_{min}, T_{max}, Kel, AUC_{0-24}, AUC_{0-t}, AUC_{0-168}, $AUC_{0-\infty}$.

2.2.2 Secondary Endpoint

- Exposure to risperidone, 9-hydroxyrisperidone and active moiety as assessed from C_{max}, T_{max}, AUC_{0-24}, AUC_{0-t}, $AUC_{0-\infty}$ after switching from IR risperidone to LYN-005.

2.2.3 Exploratory Endpoint

- PK modelling of risperidone, 9-hydroxyrisperidone and active moiety exposure.

3 STUDY DESIGN

3.1 Study Design and Population

LYN-005-C-004 is a blinded, multiple-dose, randomized, parallel group, safety, tolerability and PK study of LYN-005 in subjects with a primary diagnosis of schizophrenia or schizoaffective disorder in general good health.

Eligible subjects must be clinically stable and receiving a therapeutic dose of an approved oral antipsychotic drug for a minimum of 6 weeks at the time of Screening. Enrolled subjects will be evaluated under steady-state conditions on commercially-available IR risperidone tablets and then assigned in blinded fashion either to LYN-005 weekly or continued encapsulated IR risperidone daily for 3 weeks to attain (or continue) steady-state exposure.

3.2 Randomization and Blinding

A total of 32 subjects will be randomized to receive either LYN-005 (14 or 28 mg weekly) or continue receiving IR risperidone (2 or 4 mg/day). Randomization will be performed in a 3:1 ratio in a blinded fashion. Twenty-four subjects are randomized to receive LYN-005 (N=12 receiving 14 mg weekly and N=12 receiving 28 mg weekly) and 8 subjects to continue receiving IR risperidone (N=4 receiving 2 mg/day and N=4 receiving 4 mg/day). The dose of LYN-005 or IR risperidone administered will be based on the patient's current antipsychotic medication dose. Although treatment assignment is blinded; the dose level is not blinded. To maintain the blind, all subjects will either receive LYN-005 and IR risperidone-placebo or LYN-005-placebo and IR risperidone.

Subjects who successfully complete the admission procedures on Day -2 will be randomized on Day 1, using an Interactive Response Technology (IRT) system, to one of the 2 treatment groups.

3.3 Sample Size Considerations

This study is exploratory in nature and therefore not designed to test hypotheses. Approximately 32 subjects of whom 24 will receive LYN-005 will be enrolled in the study. Subjects who discontinue prematurely may be replaced at the Sponsor's discretion.

3.4 Safety Monitoring Committee

There is a planned safety review of interim, blinded safety data including PK by the Investigator and Medical Monitor once data through Day 14 are available from 12 subjects. The safety data reviewed will include adverse events, vital signs, laboratory data, suicidality, and illness severity. Additionally, the PI or Sponsor may request an ad hoc review of blinded safety information, e.g., serious adverse events, at any time during the study.

3.5 Interim Analysis

No interim analysis is planned for this study.

3.6 Timing of Analyses

The final analysis will occur when the last subject completes the end-of-study visit (Day 35) and the database has been locked and unblinded.

4 DATA ANALYSIS CONSIDERATIONS

All analyses will be conducted based on SAS 9.4 or higher. PK analyses will be performed in Watson LIMS (version 7.5).

All data in the database will be presented in by subject data listings.

Unless otherwise stated, all listings will be sorted by randomized treatment group, dose level, subject ID, treatment period, and time point (and time, if available).

In general, continuous data will be summarized based on n, mean, median, standard deviation (SD), minimum value, and maximum value. Categorical data will be summarized by counts and percentages. Percentages will be derived from the number of subjects in the population of interest. Counts of zero will be presented without percentages.

The following levels of precision for reporting data will be applied:

- Mean, Median: one additional decimal place to that reported for Minimum and Maximum
- SD: two additional decimal places than the Minimum and Maximum
- Percentages <100% will be reported to one decimal place. Percentages of 100% will be reported with no decimal place.

All data up to the time of study completion/withdrawal from the study will be included in the analysis. Unscheduled visits will be included in listings only.

Numbering for data displays will be based on ICH E3[(1)].

4.1 Stratification and Covariates

Subjects will be split into 2 groups based on their IR risperidone run-in dose prior to randomization. A maximum of 16 subjects in each group will be enrolled and randomized. Subjects receiving 2 mg/day IR risperidone will be randomized (3:1 ratio) to receive either 14 mg/week LYN-005 (N=12) or continued 2 mg/day IR risperidone (N=4) and those receiving 4 mg/day IR risperidone will be randomized (3:1 ratio) to receive either 28 mg/week LYN-005 (N=12) or continue with 4 mg/day risperidone (N=4), respectively.

4.2 Evaluation of Subgroups

There are no formal plans for examining subgroups. Subgroups may be identified during PK modelling.

4.3 Multiple Comparisons and Multiplicity

No formal hypothesis testing will be performed, Type 1 error will not be addressed.

5 GENERAL DATA HANDLING CONVENTIONS

5.1 Assigned and Actual Treatment

As described in Section 3.2, subjects will be randomized to LYN-005 or IR risperidone. The randomized treatment assignments will be used for listings as well as selected analyses indicated for the Safety Population.

Actual treatment groups are based on exposure data to treatment received and will be the basis for all safety and PK analyses.

The following 2 treatment groups (actual or as-randomized) are planned in this study:

- LYN-005
- IR risperidone

Within the treatment groups, there will be 2 dose levels:

- LYN-005 → 14 mg
- LYN-005 → 28 mg
- IR risperidone → 2 mg
- IR risperidone → 4 mg

5.2 Reference Dates

The following reference definitions will be applied for this study:

- Screening date is defined as the eCRF provided date on which a subject was screened for trial entry.
- Informed consent date will be the reference date for prior history data reporting.

- Enrollment date is defined as Study Day -2, date subject is admitted into the Clinical Research Unit (CRU)
- Run-in Period date is defined as the date of first dose of IR risperidone during the run-in period starting on Day -13. This data will be collected in the Case Report Form (CRF).
- Double-blind Period date is defined as the date of first dose of randomized treatment on Day 1.
- AEs allocated to the IR Run-in Period will be based on the date of first dose in the Run-in Period as the reference date.
- TEAEs will be based on the first dose of randomized treatment in the double-blind period as the reference date.
- Study day will be based on the first dose of randomized treatment in the double-blind period as the reference date.
- On-therapy Period 1 (OTP1) start date is defined as the date subject received first dose of randomized treatment on Day 1.
- On-therapy Period 2 (OTP2) start date is defined as the date subject received second dose of randomized treatment on Day 8.
- On-therapy Period 3 (OTP3) start date is defined as the date subject received third dose of randomized treatment on Day 15.
- Follow up Period (FUP) start date is defined as the date subject resumes prior antipsychotic drug on Day 22.

5.3 Study Day and Duration Variables

Reference date calculations will generally be defined as the following, assuming non- missing dates:

- Datetime of interest – reference datetime;
- If time is not available, date will be used.
    - Date of interest – reference date + 1 when the date of interest ≥ reference date;
    - otherwise, date of interest – reference date.

Date imputation will be performed as identified in Section 5.6. Otherwise, if either date is missing, reference date calculations will not be performed.

For instance, study day will be based on the first randomized dose date as the reference date. Study day will either have a negative value if collected before dosing or a positive value if collected on or after the day of first randomized dosing; there will be no study day zero.

Duration of time is dependent on reference dates and will be calculated in a manner similar to that of the reference date calculation, assuming that dates of interest will strictly follow reference dates (e.g. no negative values). For example, duration on study will use date (not datetime) and is defined as the end of study date – screening date + 1.

5.4 Study Time Periods

Safety reporting will be classified by the following study periods for analysis:

- Screening Period is defined as the period between Day -21 and Day -14: pre-dose (Screening visit date up to the day before Run-in IR dosing).
- Run-in Period is defined as the period between Day -13 and Day -1: pre-dose (First Day of IR dosing to Day -1).
- Double-blind Period is defined as the period between Day 1 to Day 35 (Day of first dose of randomized treatment to end of study).
- OTP1 is defined as the period between Day 1 and Day 7 (prior to dosing on Day 8)
- OTP2 is defined as the period between Day 8 and Day 14 (prior to dosing on Day 15)
- OTP3 is defined as the period between Day 15 and Day 21.
- FUP is defined as the period between Day 22 and Day 35.

5.5 Baseline and Post-Baseline Changes

Unless stated otherwise, baseline and post-baseline change values will be based on the following:

Baseline values will be based on the last assessment performed prior to the first randomized treatment dose. Unscheduled/repeat assessments performed prior to ER dosing in the CRU on Day 1 can be used as baseline values should the planned assessment result in a missing value. Post-baseline values will be those collected after the first dose of randomized treatment.

Change from baseline is defined as: post-baseline value – baseline value.

5.6 Imputation of Partial Dates

Appendix 1 details partial date conventions that will be used for the determination of treatment-emergent adverse events, and prior and concomitant medications.

End of Study Date

Missing study end dates will not necessarily be imputed at the end of the study. However, in the event of an ongoing reporting need, end of study dates may be imputed as the earliest of the data cutoff date, date of death, or last date recorded on the CRF.

5.7 Multiple Assessments and Visit Windows

Nominal visits (e.g. those identified by the study CRF) will be the basis of summarization; no visit date windowing will be conducted. Unscheduled data will be included in subject data listings.

5.8 Missing Data

AE and concomitant medication partial date imputations are described in Appendix 1. Imputing partial dates will only be used to identify if the AE is a TEAE or not, or if a collected medication is prior or concomitant. Otherwise, missing data will not be imputed. In the listings, the true CRF collected date will be reported. With respect to PK data, parameters will be derived as defined in Section 7.1 and although these methods may employ some inherent estimation of missing values (i.e., calculation of AUC), no formal imputation methods will be performed for the study.

6 STUDY SUBJECT DATA

6.1 Analysis Populations

Enrollment Set (ENR): Defined as all subjects who are enrolled in the study and admitted to the research unit on Day -2. The Enrollment Population will be the primary set used for disposition, demographic and baseline characteristic data reporting.

Safety Population (SAF): Defined as all enrolled subjects who are randomized to study drug (LYN-005 14mg/28mg or IR Risperidone 2mg/4mg) and receive at least one dose of randomized study drug. Subjects will be reported according to the treatment received. The Safety Population will be the primary safety analysis population.

PK Population: Defined all enrolled subjects who receive at least one dose of randomized study drug and have at least 1 post-dose quantifiable (or evaluable) PK concentration data. Additional analysis sets within the PK population, if identified, will be specified in the PK Analysis Plan.

6.2 Subject Disposition

Summaries of number of subjects screened, analysis population membership, number of subjects who received IR risperidone run-in and weekly treatment dose, and final subject status (completed, discontinued), including reasons for withdrawal, will be produced based on the ENR Set.

Analysis populations, weekly treatment dosing, and final subject disposition status will be listed.

6.3 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Protocol deviations may be defined as exclusionary from the analysis according to protocol objectives and endpoints. Prior to the final analysis of the study data, subjects with exclusionary protocol deviations will be identified and specified for each analysis set and documented. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g., early termination. Any protocol deviations related to COVID-19 will be documented.

A listing of major protocol deviations will be provided for all enrolled subjects. A listing of COVID-19 protocol deviations will be provided for the ENR Set.

6.4 Demographic and Baseline Characteristics

Subject demographics will be summarized and listed for the ENR Set. These will include age in years, sex, ethnicity, race, baseline height (cm), baseline weight (kg), and baseline BMI (kg/m^2) calculated from baseline height and baseline weight. Age will not be calculated and will come directly from the Case Report Form (CRF).

Total scores collected from PILL-5, Extrapyramidal Symptom Rating Scale (ESRS), Clinical Global Impression – Severity (CGI-S), Columbia Suicide Severity Rating Scale (C-SSRS) ideation past 6 months, C-SSRS behavior lifetime, C-SSRS aborted attempts lifetime, C-SSRS interrupted attempts lifetime, and C-SSRS actual attempts lifetime at Screening will be summarized. Total scores collected from ESRS, CGI-S, C-SSRS ideation past 6 months, C-SSRS behavior lifetime, C-SSRS aborted attempts lifetime, C-SSRS interrupted attempts lifetime, and C-SSRS actual attempts lifetime will be included as baseline characteristics, and will be summarized.

6.5 Medical History

Medical History will be coded based on the Medical Dictionary for Regulatory Activities (MedDRA) for reporting by system organ class (SOC) and preferred term (PT).

A listing of medical history will be provided for all subjects in the ENR Set.

6.6 Psychiatric History

Primary diagnosis of schizophrenia or schizoaffective disorder, years since primary diagnosis, years since last hospitalization for worsening of schizophrenia, previously hospitalized, and prior documented tolerability to IR risperidone will be summarized. Total scores collected from the Structured Clinical Interview-Positive and Negative Syndrome Scale (SCI-PANSS) questionnaire at Screening will be summarized.

All psychiatric history data will be listed for subjects in the ENR Set.

6.7 Prior and Concomitant Medication

Prior medications are those which have been identified to have been discontinued prior to admittance into the CRU on Day -2. Concomitant medications are those which have been identified to have been taken at any point after admittance into the CRU. For study day calculations, the reference date will be the Day -2 date.

All prior and concomitant medication data will be listed for subjects in the ENR population and will include the verbatim and preferred drug name and WHO Drug Dictionary anatomic therapeutic class (ATC) Level 2 classification (i.e. therapeutic main group). A flag for concomitant medications to identify in which study period the medication was taken will be provided.

6.8 Study Drug Exposure

The number and percent of subjects receiving IR dosing and randomized treatment will be displayed. Number of days in the study and IR dosing compliance will be summarized. This study drug exposure will be presented for SAF subjects.

Listings of study drug administration will be produced for the SAF population.

6.8.1 Gastrointestinal [redacted] Imaging

Gastrointestinal (GI) [redacted] of LYN-005 will be reported based on the SAF Population.

[redacted]

A listing of abdominal X-ray data, [redacted] will be provided for the Imaging population.

7 PHARMACOKINETICS

7.1 Pharmacokinetic Parameters

Blood samples for PK assessments will be collected as outlined in the Schedule of Events of the protocol (dated 29AUG2020 V2, section 18.1, Schedule of Events). Plasma concentrations of risperidone, 9-OH-risperidonerisperidone and the active moietyactive moiety will be summarized using the PK Population for each assessment timepoint by treatment, dose level and day. Summary profiles will be plotted over time by treatment, dose level and day with the concentration axis displayed on a linear scale and on a logarithmic scale. Individual drug plasma concentrations will also be plotted over time. Further details will be provided in the PK analysis plan.

8 SAFETY

All safety analysis reporting will be based on the SAF Population unless otherwise stated.

8.1 Adverse Events

Adverse events (AEs) will be recorded from the time the subject signs informed consent until the end of study (Day 35 or upon discontinuation). Treatment-emergent AEs are defined as an event that occurs after first receipt of randomized treatment on Day 1, or a pre-existing condition that worsens in severity or becomes serious after first receipt of randomized treatment on Day 1. For study day calculations, the reference date will be the Day 1 date. All AEs will be coded based on the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) at time of study start.

An overview of AEs will be produced for Run-in and Double-blind study periods as defined in section 5.4, treatment, dose, and overall active. The overview will include counts and percentages of subjects and events with any incidences of: treatment-emergent AEs (TEAEs), TEAEs related to study treatment, maximum severity of adverse events (i.e., either mild, moderate, or severe), TEAEs leading to study withdrawal, serious adverse events (SAEs), and fatal AEs.

A similar overview of TEAEs will be produced by On-Therapy weekly dose, as well as, for specific time intervals post-LYN-005. Time intervals for AEs reported between these periods will be presented for each of the on-therapy periods.

- Within 24 hours post-LYN-005 (0 hours ≤ and ≤ 24 hours),
- Between 24 and 48 hours post-LYN-005 (24 hours < and ≤ 48 hours),
- From 48 hours to EOS (>48 hours to EOS).

The number and percent of subjects experiencing the following AEs will be summarized for each on therapy period, follow-up period, and overall by system organ class (SOC) and preferred term (PT) in descending order of overall incidence. For these summaries, subjects will be counted once within each SOC and PT.

- TEAEs
- TEAEs related to study treatment
- TEAEs leading to study withdrawal
- SAEs.

A conservative approach for missing AE severity and relationship will be taken. AE with missing severity will be assumed to be severe and AEs with missing relationship will be assumed to be related to active drug. As relationship to LYN-005 and relationship to IR risperidone are both collected in the eCRF, the following reporting structure will be followed. If an AE is marked as related to both IR risperidone and LYN-005, as the study is blinded, the relationship will be assumed to be related to active drug (ie: if marked as related to LYN-005 (active) and related to IR risperidone (placebo) the AE will be reported under LYN-005). If an AE is marked as not related to either IR risperidone or LYN-005, the TEAE will be assigned to active drug. If the event is related to the placebo and not to active, the event will be reported under the placebo and vice versa for active treatment relationship.

A comprehensive listing of all reported AEs will be provided in a by-subject data listing for the ENR Population. In addition, the following listings will be provided:

- SAEs
- TEAEs leading to study withdrawal
- Fatal AEs

8.2 Psychiatric Assessments

8.2.1 Structured Clinical Interview-Positive and Negative Syndrome Scale (SCI-PANSS)

The SCI-PANSS is a 30-item scale used to evaluate the presence, absence and severity of Positive, Negative and General Psychopathology symptoms of schizophrenia accompanied by a semi-structured interview. In this study, the PANSS will be used at baseline in order to assess the stability and severity of subjects' disease. Each of the 30 items in the PANSS has a definition

and a basis for rating, and all items are rated on a 7-point scale (1 = absent; 7 = extreme). Subjects' PANSS scores at Screening must be aligned with stable, mild to moderate disease based on values of <4 for individual items P1, P3, P4, P6, P7 and G14. The strengths of the PANSS include its structured interview, robust factor dimensions, reliability, the availability of detailed anchor points, and validity.

PANSS will be administered to all subjects at screening.

PANSS total score data will be provided in data listings and presented for all subjects in the SAF.

8.2.2 Clinical Global Impression – Severity (CGI-S)

The CGI-S measures the severity of a subject's psychopathology. As efficacy is not assessed in this study, the CGI-S will be used to assess subject stability at screening, enrollment and throughout the study. Scores are as follows:

1. Normal, not ill at all
2. Borderline mentally ill
3. Mildly ill
4. Moderately ill
5. Markedly ill
6. Severely ill
7. Among the most severely ill subjects

Observed values and changes from baseline for CGI-S total score will be summarized for each time point collected for subjects in the SAF.

All CGI-S data will be presented in data listings for all subjects in the SAF.

8.2.3 Assessment of Suicidal Ideation and Behavior – Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is an interview-based rating scale intended to systematically assess suicidal ideation and suicidal behavior. Two versions of the C-SSRS will be utilized in this study to ensure subject safety; Baseline/Screening and Since Last Visit assessments.

At the Screening Visit, the Baseline/Screening version will be used to assess study eligibility criteria and baseline suicidal ideation and behavior. Each subsequent assessment will utilize the Since Last Visit version of the C-SSRS.

The C-SSRS will be administered to all subjects to monitor stability at multiple predefined visits and at the discretion of the PI.

Observed values and changes from baseline for C-SSRS ideation past 6 months score will be summarized for maximum ideation score during the DBP collected for subjects in the SAF. Observed values and changes from C-SSRS preparatory acts or behavior lifetime, C-SSRS aborted attempts lifetime, C-SSRS interrupted attempts lifetime, and C-SSRS actual attempts

lifetime at baseline will be summarized for behavior score during all OTP collected for subjects in the SAF.

All C-SSRS data will be presented in data listings for all subjects in the SAF.

8.3 Clinical Laboratory Evaluations

Clinical chemistry and hematology parameters will be reported based on the International System of Units (SI). The following laboratory evaluations will be reported in data summaries: Hematology, Coagulation, Clinical Chemistry, Urinalysis.

Observed values and changes from baseline for continuous laboratory evaluations, including hematology, clinical chemistry, and coagulation will be summarized for each time point for subjects with clinically significant results collected for SAF. See Section 5.5 for the baseline definition.

All laboratory parameters will be provided in subject data listings for the SAF population.

Results from urine drug screening (benzodiazepines, cocaine, opiates, cannabis, and other), Serology lab assessments (Hepatitis B, Hepatitis C, HIV), *H. pylori* breath test, Compliance lab assessments (Alcohol breath test), Nicotine History, Pregnancy results (serum and urine), and CYP2D6 genotype will be provided in subject data listings for the SAF population.

8.4 Other Safety Evaluations

8.4.1 Extrapyramidal Symptoms – Extrapyramidal Symptom Rating Scale (ESRS)

The Extrapyramidal Symptom Rating Scale (ESRS) will be used at baseline and throughout the study in order to assess the severity of and monitor extrapyramidal symptoms. The ESRS consists of several components:

- a questionnaire of EPS or DIMD;
- an examination of Parkinsonism and akathisia;
- an examination of dystonia;
- an examination of dyskinesia;
- clinical global impression severity (CGI-S) scales of tardive dyskinesia, Parkinsonism, dystonia and akathisia.

Observed values and changes from baseline for ESRS total score will be summarized for each time point collected for subjects in the SAF. See Section 5.5 for the baseline definition.

All ESRS data will be presented in data listings for all subjects in the SAF.

8.4.2 Vital Signs

Vital signs include: respiratory rate (bpm); temperature (ºF); systolic and diastolic blood pressure (mmHg); heart rate (beats/min). Observed values and changes from baseline for vital signs will

be summarized for each time point collected for subjects in the SAF. See Section 5.5 for the baseline definition.

All vital signs data will be presented in data listings for all subjects in the SAF.

8.4.3 Electrocardiogram (ECG)

Electrocardiogram (ECG) parameters include: HR (beats/min), PR (msec), QRS (msec), QT (msec), QTcF (msec). Observed values and changes from baseline for ECG parameters will be summarized at each time point for subjects in the SAF.

The number and percent of subjects with specified evaluation of QTcF values will be summarized overall for the DBP (using all evaluations, including unscheduled assessments) and by visit. The QTcF evaluations consist of:

- Absolute QTc interval prolongation:
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from baseline in QTc interval:
  - QTc interval increases from baseline > 30
  - QTc interval increases from baseline > 60

All ECG data will be presented in data listings for all subjects in the SAF.

8.4.4 Physical Examinations

A general physical examination will be performed at Screening, Day -2 and the EOS visit. Physical examinations will be presented in subject data listings for all subjects in the SAF.

8.4.5 Prolactin

Samples to assess Prolactin will be performed at Screening, Day 1, Day 8, Day 15, Day 21, and the EOS visit. Observed values and changes from baseline and from screening for Prolactin will be summarized at each time point for subjects in the SAF.

Prolactin results will be presented in subject data listings for all subjects in the SAF.

8.4.6 Acid Reflux Severity Scale

The acid reflux severity scale is performed during screening to ensure compliance with exclusion criteria. Data will be listed for all subjects in the SAF.

8.4.7 Fecal Occult Blood Test

Observed values and changes from baseline for fecal occult blood tests will be summarized for each time point for subjects in the SAF population. See Section 5.5 for the baseline definition.

Fecal occult blood test details will be presented in subject data listing for all subjects in the SAF.

9 CHANGES TO THE PLANNED ANALYSIS

No changes from the analyses in the protocol are planned.

10 REFERENCES

(1) International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports E3. Step 4. 1995.
https://database.ich.org/sites/default/files/E3_Guideline.pdf

11 APPENDICES

11.1 APPENDIX 1. Partial Date Conventions

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < Day 1 randomized treatment dose date, then not TEAE If start date ≥ Day 1 randomized treatment dose date, then TEAE
Partial, but known components show that it cannot be on or after Day 1 randomized treatment dose date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after Day 1 randomized treatment dose date	Known	If stop date < Day 1 randomized treatment dose date, then not TEAE If stop date ≥ Day 1 randomized treatment dose date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < Day 1 randomized treatment dose date, then not TEAE If stop date ≥ Day 1 randomized treatment dose date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < Day 1 randomized treatment dose date, then not TEAE If stop date ≥ Day 1 randomized treatment dose date, then TEAE
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < Day 1 randomized treatment dose date, then not TEAE If stop date ≥ Day 1 randomized treatment dose date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant
	Missing	If stop date is missing, but ONGOING reported, assign as concomitant If stop date is missing, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant
	Missing	If stop date is missing, but ONGOING reported, assign as concomitant If stop date is missing, assign as concomitant
Missing	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant
	Missing	If stop date is missing, but ONGOING reported, assign as concomitant If stop date is missing, assign as concomitant

11.2 APPENDIX 2: Tables, Listings, and Figures

All tables, listings, and figures will be numbers according to the ICH-E3 Guideline. A table of contents containing the tables and listings to be produced based on the SAP text are included in a separate mock shell document appended to the SAP.