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HSY244

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CHSY244X2201

A randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with atrial fibrillation

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) CCI for trial **CHSY244X2201.**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

The study protocol (v04) was available at the time of finalization of this Statistical Analysis Plan Amendment 1.

1.3 Study objectives

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
• To evaluate the efficacy of HSY244 to restore sinus rhythm in participants with AF	• Conversion to sinus rhythm for at least 1 minute within 90 minutes from the start of study drug administration
Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To evaluate the safety and tolerability of HSY244 in participants with AF	• Results of safety assessments including adverse events, vital signs, ECG parameters, and laboratory assessments of blood and urine.
• To evaluate the pharmacokinetics of HSY244 in participants with AF	• HSY244 plasma AUClast, Cmax, and Tmax after i.v. administration
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)

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Objective(s)	Endpoint(s)

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1.4 Study design and treatment

This is a randomized, placebo-controlled, investigator- and participant-blinded study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of HSY244 in participants with AF. An initial cohort (Cohort 1) of approximately 29 participants (approximately 20 participants receiving HSY244) is planned to be enrolled to evaluate a single 150 mg i.v. dose of HSY244 for AF cardioversion to sinus rhythm.

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Participants with AF that meet clinical criteria for direct current cardioversion will be screened, and on Day 1, after eligibility is confirmed, administration of a 15 minute i.v. infusion of HSY244 or placebo will occur. Participants will then be monitored for cardioversion to sinus rhythm. For those remaining in AF after 90 minutes, direct current cardioversion can be performed. Participants will be monitored for at least 3 hours, although overnight observation will be available. Participants will be evaluated for safety and pharmacokinetic assessments during end of study assessments, which are to occur on Day 5 (96 hours post dose) ± 24 hours.

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2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

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The FIR will focus on the following analyses:

1. Participant Disposition
2. Demographics and baseline characteristics by cohort. Baseline characteristics include, but not limited to: age, sex, race, ethnicity, BMI, relevant medical history/current medical conditions (previous diagnosis of heart failure, etc.), duration of current AF episode, etc.
3. Safety Results
    a. Number and percentage of adverse events by body system and Cohort
    b. Number and percentage of adverse events by preferred term and Cohort
4. Pharmacokinetic results for each Cohort
5. Pharmacodynamic analyses include, but are not limited to:
    a. Fisher's exact test comparing conversion rates between HSY244 and placebo
    b. MMRM analysis of ECG and heart rate parameters comparing HSY244 and placebo
    c. Concentration effect analysis of QT and Heart Rate parameters
    d. Time to event analysis for the time to conversion and time in sinus rhythm after conversion comparing HSY244 and placebo
    e. AF burden comparison between HSY244 and placebo

3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

The safety analysis set will include all participants that received any investigational product.

The PK analysis set will include all participants with at least one available valid PK concentration measurement, who received any investigational product and with no protocol deviations that impact on PK data.

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The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

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If updates to Table 4-1 are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

All participants within the PK analysis set will be included in the PK data analysis.

5.1 Variables

The PK variables of interest are:

- AUClast: the AUC from time zero to the last measurable concentration sampling time (tlast)
- Cmax: The maximum (peak) observed plasma drug concentration after single-dose administration
- Tmax: The time to reach maximum (peak) plasma drug concentration after single dose administration (time)

5.2 Descriptive analyses

HSY244 plasma concentration data will be listed by treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated as described in Section 5.1 and will be listed by treatment and participant. Additional parameters may be estimated as relevant. Graphical methods will be employed to show mean and individual concentration-time profiles.

5.3 Statistical model, assumptions and hypotheses

Not applicable

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective is to evaluate the efficacy of HSY244 to restore sinus rhythm in participants with AF.

6.1.1 Variables

The primary endpoint will be conversion to sinus rhythm for at least one minute within 90 minutes after the start of study drug administration (yes or no). Only participants that complete treatment will be included in the primary analysis. If a participant has been monitored for at least 45 minutes and is not converted to sinus rhythm, the primary endpoint will be defined as 'no'. If a participant converts to sinus rhythm at any time during the post-treatment 90 minutes observation period, regardless of the length of time monitored, the primary endpoint will be defined as 'yes'. Participants with a non-missing primary endpoint value will be included in the primary analysis regardless of their study disposition e.g. loss to follow up, early termination, etc.

6.1.2 Descriptive analyses

The observed proportion of participants converted to sinus rhythm within the first 90mins of observation will be reported for each treatment and cohort. The observed proportion of participants that are electrcardioverted after the 90mins observation period will also be reported for each treatment and cohort.

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6.1.3 Statistical model, assumptions and hypotheses

The conversion rates between HSY244 and placebo will be compared using Fisher's Exact test. This will test a null hypothesis that the conversion rate is the same for HSY244 and placebo. The conversion rates for each treatment and the exact 80% confidence intervals will be reported. The difference in the conversion rates between HSY244 and placebo will be reported along with the 80% confidence limits for the difference, as well as the odds ratio, the 80% CI for the odds ratio, and the associated p-value.

The impact of duration of current atrial fibrillation episode (< 48 hours, 48 hours - 7 days, 7 - 14 days, 14 - 30 days, and 30-60 days) on conversion rate will be investigated in a supporting analysis. The impact of length of time of known atrial fibrillation diagnoses on conversion rate will also be explored in a supporting analysis (e.g. < 1 year, 1 – 5 years, 6 - 10 years, >10 years, and quartiles of length of atrial fibrillation diagnosis).

All analyses will be performed separately for Cohort 1 CCI
Placebo participants from the two cohorts may be pooled for summaries and analyses if it is deemed appropriate. Only participants who complete study treatment will be included in the primary analysis.

6.1.3.1 Model checking procedures

Not applicable

6.1.3.2 Graphical presentation of results

Results will be displayed tabular and graphically, where the conversion rate (80% CI) for each treatment will be displayed in dot plots and a forest plot.

6.1.3.3 Sensitivity analysis

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6.1.3.4 Supplementary analysis

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6.2 Secondary objectives

There are no secondary PD objectives.

6.3 Exploratory objectives

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6.3.1 Variables

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6.3.2 Descriptive analyses

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6.3.3 Statistical model, assumptions and hypotheses

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6.3.4 Graphical presentation of results

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7 Statistical methods for safety and tolerability data

The secondary safety objectives are to evaluate the safety and tolerability of HSY244 in participants with AF.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), laboratory measurements, as well as participant demographics, baseline characteristics, and treatment information.

The values for the ECG intervals (PR interval, QRS duration, heart rate, RR, QT, QTcF). For these ECG parameters described, the central reader values will be used for analysis. These parameters will be derived from the single time point ECG data.

Heart rate will be analyzed using both the safety analysis dataset and the PD analysis dataset.

7.2 Descriptive analyses

Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group and cohort for the safety analysis set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by treatment group and cohort. For AF disease history, if the start month is missing, then the start month will be imputed as 'JAN'. Similarly, if the start day is missing, the start day will be imputed as '01'.

Treatment

Data for study drug administration (rescue medication), concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system by treatment group and cohort.

Vital signs

All vital signs data will be listed by treatment group, cohort, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment, cohort and visit/time.

ECG evaluations

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from single time point ECGs for each participant during the study. ECG data will be read and interpreted locally for initial safety readouts. The single time point ECGs will be read centrally for the parameters above and these will be reported in the CSR.
2. Categorical Analysis of QT/QTcF interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced (by treatment group).

QT/QTcF and QRS duration will be examined separately between individuals with and without a complete bundle branch block.

All ECG data will be listed by treatment group, cohort, participant, and visit/time, and abnormalities will be flagged.

Summary statistics will be provided by treatment, cohort and visit/time.

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These descriptive statistics will be generated for all observations, observations where participants are in AF and observations where participants are in sinus rhythm.

The MMRM and concentration-effect analyses described in Section 6.3.3 may also be used for the ECG parameters described above.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, participant, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a participant with any abnormal values. Summary statistics will be provided by treatment, visit/time and cohort.

Adverse events

All information obtained on adverse events will be displayed by treatment, participant and cohort.

The number and percentage of participants with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A participant with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

The number and percentage of participants with adverse events by maximum severity or severity of adverse events may be tabulated by body system and preferred term with a breakdown by treatment, if deemed necessary.

The number and percentage of participants with serious adverse events may be tabulated by body system and preferred term with a breakdown by treatment, if deemed necessary.

The number and percentage of participants with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment.

Seizure related adverse events (based on SOC and/or PT) will be listed and summarized separately as AEs of special interest. The number and percentage of participants with such adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

Only adverse events that will occur at or after first drug intake (i.e., treatment emergent AEs) will be included in the AE summaries.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Other safety evaluations

Not applicable

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameters) may be created.

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