Statistical Analysis Plan

An Open-label, Single-dose, Randomized, Two-way, Two-period Crossover Study to Compare the Pharmacokinetics and Bioavailability of a Novel Furosemide Regimen Administered Subcutaneously Versus the Same Dose (80 mg) Administered Intravenously in Subjects with Chronic Heart Failure

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ABBREVIATIONS

AE	Adverse Event(s)
AESI	Adverse Event(s) of Special Interest
AUC	Area Under the Curve
AUC0-24	Area Under the Curve from Time 0 (Pre-Dose) to 24 Hours Post-Dose
AUCinf	Area Under the Curve from Time 0 to infinity
AUClast	Area Under the Curve from Time 0 to the last measurable plasma concentration
BLQ	Below Limit of Quantification
BMI	Body Max Index
Cmax	Maximum Plasma Concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
DDE	Drug Dictionary Enhanced
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary of Regulatory Activities
N	Sample Size
NYHA	New York Heart Association
PI	Principle Investigator
PK	Pharmacokinetic(s)
PD	Pharmacodynamic(s)
RLD	Reference Listed Drug
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
T½	Half-Life
TEAE	Treatment-Emergent Adverse Events
Tmax	Time to Maximum Plasma Concentration
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analysis and reporting of the safety, pharmacokinetic (PK), and pharmacodynamic (PD) results for Study SQI-01-01. This study will determine the comparative bioavailability of subcutaneous infusion of a novel formulation of furosemide (80mg in 2.7mL) to the reference listed drug (RLD), Furosemide Injection (10 mg/mL), USP (Hospira, Inc., Lake Forest, IL, USA) (Furosemide Injection 2011) administered by IV bolus. This study will be an open-label, single-dose, randomized, two-way, two-period crossover study in 20 adult subjects previously diagnosed with mild to moderate heart failure (New York Health Association [NYHA] class II/III) being treated with oral furosemide therapy at a dose of ≥40 mg/day.

In consultation with the FDA (PIND 1437480, it was decided to compare the subcutaneous administration of the investigational formulation with a single bolus of 80mg furosemide over 2 minutes. This is the way the product is most commonly administered clinically. The current label for furosemide injection, USP lists administration of two doses of 40mg two-hours apart. The dosage instructions for the divided administration date back to the 1968 package insert of the innovator drug (LASIX, NDA 016363), and is not known to be in use in the US. Because of concentration-dependent elimination, it is anticipated that the AUC of the subcutanious infusion may exceed 100% and may result in a statistical difference in favor of subcutaneous infusion. The study is not powered to show a superior diuretic response. Avoidance of a high Cmax, slower elimination and increased diuretic efficiency (mL of urine per mg of furosemide) are all considered favorable. The study is not powered for or intended to result in a claim in favor of the subcutaneous infusion.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled *Guidance for Industry: Statistical Principles for Clinical Trials* (International Conference on Harmonisation 1998) and the most recent ICH E3 Guideline entitled *Guideline for Industry: Structure and Content of Clinical Study Reports* (International Conference on Harmonisation 1995).

This SAP describes the populations, subject characteristics and safety parameters that will be evaluated. This SAP provides details of the specific statistical modeling methods that will be used to support authoring of the clinical study report (CSR). If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

2. OBJECTIVES

The primary objective of the study is:

- To estimate the absolute bioavailability of furosemide administered by 5-hour subcutaneous infusion using a biphasic delivery profile compared with an equivalent dose of furosemide administered by intravenous (IV) bolus administration.

The secondary objectives of the study are:

- To characterize the PK of furosemide administered by 5-hour subcutaneous infusion using a biphasic delivery profile.

- To characterize the PD (diuresis and natriuresis) of furosemide after administration by 5-hour subcutaneous infusion or IV.
- To characterize the tolerability of administration of furosemide by 5-hour subcutaneous infusion and by IV.

3. ENDPOINTS

The primary endpoint is the relative absolute bioavailability following 5-hour subcutaneous infusion based on a comparison of the area under the curve (AUC) of furosemide resulting from each administration (subcutaneous:IV).

The secondary endpoints are:

- PK parameters over the timeframe of 24 hours, including, but not limited to, maximum plasma concentration (Cmax), time to Cmax (Tmax), AUC from time 0 (pre-dose) to 24 hours post-dose (AUC0-24), AUC from time 0 to the last measurable plasma concentration (AUClast) and to infinity (AUCinf), half-life (t½), apparent systemic clearance and volume of distribution (subcutaneous only), and systemic clearance and volume of distribution (IV only).
- Urine volume and sodium concentration in urine collected over 8 hours and 24 hours commencing at the start of dosing.
- Infusion site pain (IV and subcutaneous administration) measured using patient reported scales, and presence of erythema and edema (subcutaneous only) both recorded through photography and assessed by the Principle Investigator (PI)/designee-reported scales.

4. STUDY TREATMENTS

Treatment A (Test):

SQIN-01 will be administered as 30 mg delivered over the 1st 60 minutes (total 1 mL), followed by 50 mg over 4 hours (total 1.7 mL). The total dosage and volume administered over 5 hours will be 80 mg and 2.7 mL, respectively.

The investigational furosemide formulation is a sulfobutyl ether β-cyclodextrin buffered solution at 30 mg/mL and at pH 7.4 (range: 7.0 to 7.8). Subcutaneous infusion will be performed using a qualified FDA cleared commercial precision syringe infusion pump, which will deliver 2.7 mL of the furosemide formulation over 5 hours, using a biphasic delivery profile. The infusion set cannula will be placed approximately at 1/3 of an imaginary line between the belly button and the frontal bottom of the rib cage (10th rib). The infusion set, location ande delivery parameters mirror administration by the SQIN-Infusor, the device constituent component of the drug-device combination product the study is designed to support.

Treatment B (Reference):

Furosemide Injection, USP (10 mg/mL) will be administered as an IV bolus over 2 minutes. The total amount of furosemide administered will be 80 mg. Administration of 80mg by IV bolus was selected in consultation with the FDA as reflected in the minutes of the pre-NDA meeting (PIND 143748) since this is the way furosemide is used most often clinically instead of the labelled divided doses (2x40mg) given two hours apart.

The RLD, Furosemide Injection, USP (Hospira, Inc., Lake Forest, IL) is provided as a sterile solution intended for intramuscular or IV administration. Each mL contains furosemide 10 mg and sodium chloride sufficient to render the solution isotonic in water for injection. Furosemide Injection, USP contains USP contains sodium hydroxide and sodium chloride (hydrochloric acid used for pH adjustment); the pH is approximately 9.0 (range: 8.0 to 9.3).

5. STUDY DESIGN

The Treatment Phase will be comprised of 2 Crossover Periods separated by a 7-day outpatient fluid re-equilibration washout (Table 5-1). Subjects will discontinue oral furosemide at least 24 hours prior to administration of study drug for each Crossover Period [e.g., no oral furosemide should be administered after 10 pm the night prior to Clinical Research Unit (CRU) admission]. Subjects will be randomly assigned in a 1:1 ratio to 1 of 2 treatment sequences (AB or BA) to receive both subcutaneous furosemide (Treatment A; Test) and IV furosemide (Treatment B; Reference) in Crossover Periods (i.e., subcutaneous followed by IV or vice versa). Subjects will remain domiciled in the CRU for each treatment Period during the Treatment Phase through 24 hours after administration of study drug, after which time they will be discharged from the CRU if safety parameters are acceptable to the Investigator. Oral furosemide therapy will be re-initiated at discharge after Treatment 1 (i.e., during the 7-day fluid re-equilibration washout) and after Treatment 2 (i.e., between discharge and Follow-up phone call).

The Follow-up Phase will occur 7 days (±1) after discharge from the CRU following Treatment 2, completing subjects' study participation.

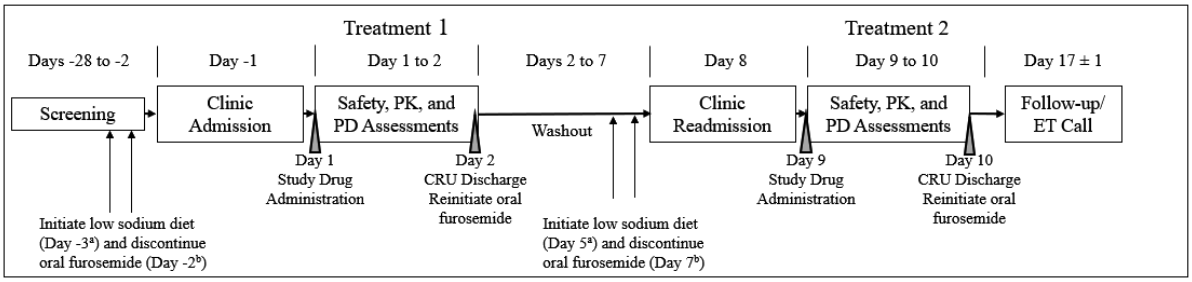
Table 5-1. Treatment Sequences

Treatment Sequence	Treatment 1	Washout	Treatment 2
	Day 1	Day 2-8	Day 9
Sequence AB (n=10)	A	Oral Furosemide	B
Sequence BA (n=10)	B	Oral Furosemide	A
Treatment A: SQIN-01 Treatment B: Furosemide Injection, USP			

Subjects will be screened within the 28 days (Day -28 to -3 Screening Visit) prior to admission to the CRU on Day -1 (the day prior to dosing) for pre-dose assessments. On the morning of Day 1 and Day 9, subjects will complete pre-dose assessments and be administered the assigned study treatment, with the start of the subcutaneous infusion or IV bolus considered to be time zero.

Subjects will remain in the CRU from Day -1 through Day 2 and Day 8 through Day 10. Study assessments will be repeated on each day that the subject remains in the CRU with the assigned treatment for the respective treatment arm. Study Completion is achieved after the subject completes his or her Follow-up phone call on Day 17 (±1 day). Figure 3-1 displays the study design schematic.

Figure 5-1. Study Design



[a] Subjects should begin avoiding salty foods (target <2 g sodium/day) at any time starting 3 days prior to CRU admission (Day -3 or Day 5).

[b] Oral furosemide should be discontinued at least 24 hours prior to study drug administration (e.g., no oral furosemide should be administered after 10 pm the night prior to CRU admission [Day -2 or Day 7]). Oral furosemide should be re-initiated at CRU discharge on Day 2 and Day 10.

Selected safety parameters will be collected pre-dose and at intervals specified in the schedule of procedures and Time & Events Schedule (See protocol, Table 1-1). Safety assessments will include adverse events (AEs), physical examinations, vital signs, and clinical laboratory evaluations. Subjects will be discharged from the CRU on Day 2 and Day 10, if safety parameters are acceptable to the Investigator. Subjects will return to the CRU for a Follow-up visit on Day 17 (±1 day) to assess any safety changes or event. Study Completion is achieved after the subject completes his or her Follow-up Phone Call.

6. PHARMACODYNAMIC ASSESSMENTS

6.1. Urine Sample Collection

Subjects should attempt to void prior to study drug administration.

Spontaneous urine samples should be collected and pooled for the following time intervals post-initiation of furosemide administration: 0 to 1 hour; 1 to 2 hours; 2 to 4 hours; 4 to 6 hours; 6 to 8 hours; 8 to 10 hours; 10 to 12 hours; 12 to 18 hours; and 18 to 24 hours.

6.2. Urine Sample Processing and Analysis

Pooled urine samples will be processed as described in the study procedures manual, and aliquots will be analyzed for sodium concentration.

7. ANALYSIS SETS

The Safety Population will consist of all randomized subjects who received at least one dose of study drug.

The PK Population will consist of all subjects who receive at least 1 dose of furosemide and have at least 1 furosemide PK concentration.

The PK Analysis Population includes all subjects in the PK Population with sufficient concentration-time data to calculate the PK profile for at least one treatment and without a protocol deviation that affects the PK profile, per the discretion of the analyst.

The PD Analysis Population includes all subjects who received at least one dose of study drug and had measurable sodium concentrations in the urine without a protocol deviation that would affect the bioanalytical results.

8. STATISTICAL ANALYSES

All statistical processing will be performed using either SAS® version 9.3 or later, SAS Studio Version 3.5 or later, or R Statistical Software (V 3.4.0 or later; R Foundation for Statistical Computing, Vienna, Austria).

Continuous safety data will be summarized with sample size (N), mean, median, standard deviation (SD), minimum, and maximum. Categorical data will be summarized with N, frequency counts, and percentages, based on N. Data will be presented for the SQIN-01 or RLD Treatment group across both Periods and overall. Demographic and baseline data will be presented across all subjects.

8.1. Baseline Characteristics and Subject Disposition

The number of subjects enrolled, included in Safety Population, and included in the PK Population will be summarized.

Demographics and baseline characteristics (age, sex, ethnicity, race, height, weight, and body mass index (BMI) will be summarized and listed individually for the Safety Population.

The numbers of subjects enrolled who complete or withdraw from the study will be summarized by Treatment group. The number of withdrawals will be further tabulated by the major reasons for discontinuation (e.g., lost to Follow-up, AE, poor compliance). A listing of subjects who discontinued due to a treatment-emergent AE (TEAE) will be provided.

8.2. Safety Analyses

All safety data will be listed by subject. TEAEs will be summarized for each Treatment by system organ class (SOC), preferred term, severity, and relationship to study drug. Observed values and changes from baseline for clinical laboratory test data, safety electrocardiograms (ECG), physical examination results, and vital signs will be summarized using appropriate descriptive statistics. The Safety Population will be used.

8.2.1. Adverse Events

AEs will be coded using Medical Dictionary of Regulatory Activities (MedDRA; Version 21.1, or later) and tabulated, including categorical information of interest such as onset and resolution time(s), treatment, time of onset relative to dosing, severity at onset, maximum severity, causal relationship to study medication, and action taken. AEs will be regarded as ‘pre-treatment’ if they occur between Screening and the time of administration of the 1st dose of furosemide and will be recorded as medical history. All other AEs that occur after the 1st dose of study medication will be considered ‘treatment-emergent’.

If an AE has a missing severity, it will be imputed as “Severe”; any missing relationship to study drug of an AE will be imputed as “Related”.

An overall summary will present the number (%) of subjects with:

- any TEAE

- any TEAE considered as related to study drug
- any serious TEAE
- any Adverse Events of Special Interest (AESI)
- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The table will also include the total number of TEAEs reported.

The AESIs for this study are defined as follows:

- Orthostatic hypotension
- Pain or discomfort associated with the infusion
- Infusion site reactions
- Events related to the Infusion System

TEAEs will be summarized by Treatment and expressed in terms of maximum severity and relationship to study medication. The incidence of TEAEs classified according to SOC will be summarized by Treatment.

All AEs will be listed.

For safety analyses, an AE will be attributed to the Period during and last treatment prior to which the onset of the AE occurred. AEs ongoing at the start of dosing in a new Treatment Period will only be counted in the new Period if worsening is noted.

8.2.2. Laboratory Evaluations

Values of hematology and blood chemistry findings will be summarized for Screening, CRU Admission (Day -1), Treatment Days (Day 1 and Day 9), Discharge Days (Day 2 and Day 10), and Follow-up Day (Day 17 (+/- 1 day). Abnormal values will be identified and flagged in the subject-level listings. Baseline is defined as the last measurement prior to dosing.

8.2.3. Vital Signs

Values of systolic and diastolic blood pressure, heart rate, temperature, and respiration rate will be presented by treatment group and Period for each assessment time and as change from pre-dose in each Period.

8.2.4. Electrocardiograms

Values of 12-lead ECG parameters (PR, RR, QRS, uncorrected QT, QTcF and QTcB) will be summarized for CRU Admission (Day -1) and Discharge (Day 10) as well as a change from Day -1 to Day 10. Abnormal values will be listed separately by subject.

8.2.5. Physical Examination Findings

All physical examination findings from CRU Admission and Study Completion will be listed.

8.2.6. Prior and Concomitant Medications

Prior or concomitant medications will be coded according to World Health Organization Drug Dictionary Enhanced (WHO DDE Sep-2018 B2, or later). All medication-related outputs will be listed for the Safety Population.

8.3. PD Analysis of Diuresis and Natriuresis

The PD analysis will evaluate the following in the PD Analysis Population:

- The urine volume output for 0-8 hours and 0-24 hours following initiation of dosing, comparing the 5-hour subcutaneous infusion of 80 mg of the investigational formulation with urine output following administration of 80 mg of Furosemide Injection, USP administered over 2 minutes by IV bolus will be summarized descriptively by dose group.
- The urinary sodium excretion for 0-8 hours and 0-24 hours following initiation of dosing, comparing the 5-hour subcutaneous infusion of 80 mg of the investigational formulation with urine output following administration of 80 mg of Furosemide Injection, USP administered over 2 minutes by IV bolus will be summarized descriptively by dose group. Urinary sodium excretion is calculated as the sodium urine concentration multiplied by the urine volume.

8.3.1. IMPUTATION OF BLQ VALUES

Sodium concentrations that are below the lower limit of quantification (BLQ) will be considered as zero.

8.3.2. SIGNIFICANT FIGURES

Urine volume, urine sodium concentration, and urinary sodium excretion will be reported to 3 significant figures.

8.4. Sample Size Selection

A sample size of 12-14 was suggested by the FDA to adequately estimate the systemic exposure of furosemide by IV bolus and SQ infusion in a replicated crossover study. A secondary objective of this study is to characterize the PD (diuresis and natriuresis) of furosemide after administration by 5-hour subcutaneous infusion or IV. In prior studies (Dormans et al. 1996, Sanjay et al. 2008, Sica et al. 2018), intra-subject variability of PD endpoints was moderately high (CV%: 24%-37%). Thus, to provide a more precise comparison of PD endpoints, a sample size of 20 was selected.

For a non-inferiority evaluation, 20 subjects will have greater than 80% power (82%) to detect a difference in a one-sided t-test with the lower margin of the 95% CI ($\alpha = 0.05$) greater than 0.8, if the observed intra-subject CV% is 27%. Additional assumptions of this calculation include:

- The bioavailability of the commercial infusion pump is the same as the IV route (F=1.0)
- The true ratio of the PD effect of furosemide by SQ infusion to IV infusion is 1.0
- There are no carry over effects with the given crossover study design

9. REFERENCES

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Sanjay S, Annigeri RA, Seshadri R, Rao BS, Prakash KC, Mani MK. The comparison of the diuretic and natriuretic efficacy of continuous and bolus intravenous furosemide in patients with chronic kidney disease. Nephrology (Carlton). 2008;13(3):247-250.

Sica DA, Muntendam P, Myers RL, et al. Subcutaneous Furosemide in Heart Failure: Pharmacokinetic Characteristics of a Newly Buffered Solution. JACC Basic Transl Sci. 2018;3(1):25-34.

10. TABLES, LISTINGS, AND FIGURES

Lists of Tables, Listings, and Figures to be generated to support the CSR are provided below. Additional Tables, Listings, and Figures may be generated, as necessary, to fully characterize and explore the available data. Text in brackets [ ] is meant to be descriptive and not appear in the caption. Text within < > refers to numbering of Tables, Listings, and Figures as per ICH Guideline for Structure and Content of Clinical Study Reports, with the "x" being a sequential number starting at 1 (i.e., 14.1.1, 14.1.2, etc.).

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