Reprieve Cardiovascular, Inc.

EU Sites: Fluid management of Acute decompensated heart failure Subjects Treated with Reprieve Decongestion Management System (DMS) – FASTR-EU Trial

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RVC-0006-EU Version 1.6

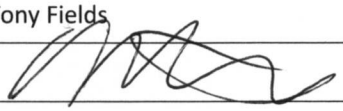
Statistical Analysis Plan

Version 1.0, 11 Apr 2024

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	11 Apr 2024	Tony Fields	Initial Release

Document Approval

Approval	
Approved By	Tony Fields
Signature	
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1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Investigation Protocol, "Fluid management of Acute decompensated heart failure Subjects Treated with the Reprieve Decongestion Management System (DMS) – FASTR-EU Trial". This SAP should be read in conjunction with the study clinical investigational plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the CIP protocol version 1.6-EU of the overall FASTR trial. While under the same parent protocol as the US-FASTR trial, the FASTR-EU trial, also known as the "Man vs. Machine Trial", is a separate study with the primary goal of testing if the Reprieve DMS is non-inferior to state-of-the-art urine sodium guided aggressive diuretic titration in two European HF centers of excellence. Although study procedures are similar, given the non-inferiority design of the current study, several differences in endpoints and analytical designs are applicable and outlined in the current document.

This study will enroll a maximum of 50 subjects randomized 1:1 to DMS and ODT across 2 clinical sites located in Europe.

Applicable Documents:

Document Number, Version	***Document Title***
RCV-0006, Version 1.6-EU	Fluid management of Acute decompensated heart failure Subjects Treated with Reprieve Decongestion Management System (DMS) – FASTR-EU Trial

2 Abbreviations

Abbreviation/Term	***Definition***
ADHF	Acute Decompensated Heart Failure
AE	Adverse Event
AT	As Treated
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRF	Case Report Form
DMS	Decongestion Management System
ODT	Optimal Diuretic Therapy
ITT	Intent-to-Treat Population
JVD	Jugular Vein Distention
JVP	Jugular Vein Pressure

KCCQ	Kansas City Cardiomyopathy Questionnaire
mITT	Modified Intent-to-Treat Population
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

3 Study Objectives

3.1 Primary Objective

The primary objective of the pilot trial is to determine if the Reprieve DMS is non-inferior in decongestion of ADHF patients with similar safety and efficacy as to a urine sodium guided aggressive diuretic therapy in heart failure centers of excellence.

Primary Efficacy Endpoint:

The primary efficacy endpoint is sodium loss per 24 hours at end of randomized therapy. (up to a maximum of 72 hours). The non-inferiority margin will be 140 mmol/24 hours, equivalent to 1kg of isotonic fluid removal.

Primary Safety Endpoint:

The primary safety endpoint is:

- clinically significant acute kidney injury defined as KDIGO stage 2 or greater AKI (≥ doubling of baseline serum creatinine or use of renal replacement therapy (RRT)),
- severe electrolyte abnormality (serum potassium < 3.0 mEq/L, magnesium < 1.3 mEq/L or sodium < 135 mEq/L),
- symptomatic hypotension, or
- hypertensive emergency.

The changes in creatinine and electrolytes will be evaluated from baseline to peak value during the maximum 72-hour study period after randomized therapy initiation. Renal Replacement Therapy (RRT) includes hemodialysis, hemofiltration, hemodiafiltration, peritoneal dialysis and kidney transplant. Isolated ultrafiltration without dialysis will not be considered RRT. Hypertensive emergency is defined as blood pressure greater than 180/120 mmHg with end-organ damage. Symptomatic hypotension is defined as sustained hypotension (< 80 mmHg systolic) with corresponding symptoms that require an intervention (i.e., fluid bolus or vasoactive medication).

3.2 Secondary Endpoints

There are two secondary efficacy endpoints and one secondary safety endpoint.

3.2.1 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be reported.

1. Net fluid loss per 24 hours at end of randomized therapy.
2. Weight loss per 24 hours at end of randomized therapy.
3. Time on IV loop diuretic from initiation of randomized therapy to last dose of IV loop diuretic administered for ADHF.
4. In hospital worsening renal function (≥ 0.3 mg/dL increase in serum creatinine) during randomized therapy.

3.2.2 Secondary Safety Endpoints

The assessment of all Device and Procedure related adverse events (AEs) and serious adverse events (SAEs) in the study population as determined by an Independent Clinical Events Committee (CEC).

The following events will not be included as a secondary safety endpoint:

- Episodes of hematuria associated with Foley catheter placement that can be adequately managed as this is an anticipated event commonly associated with Foley placement.

4 Study Design

The FASTR Man Vs. Machine trial is an open-label, prospective, multicenter, randomized, controlled pilot trial to compare the rate of decongestion for up to 72 hours with the Reprieve DMS (treatment) to the optimal diuretic therapy (control). At the two European centers participating in this trial, the SOC therapy utilized is that of the PUSH-AHF trail, which is a urine sodium guided active diuretic titration strategy proven to result in effective natriuresis. A maximum of 50 subjects will be randomized 1:1 to Reprieve DMS and ODT across these two sites.

Sites will have the opportunity to enroll subjects in an ongoing registry who meet the study criteria but refuse to participate in the trial. A maximum of 20 subjects can be enrolled in the registry per clinical site. In addition, each clinical site will have the opportunity to roll-in 2 subjects to be treated with the Reprieve DMS prior to randomization.

A CEC will be in place for the study and will be responsible for the review and adjudication of all Device and Procedure related adverse events (AEs) and serious adverse events (SAEs) as outlined in the committee charter.

Interim analysis and reporting is expected prior to all subjects completing the 90-day follow-up visit. All final study analyses will be performed when all subjects have completed the 90-day follow-up visit.

4.1 Randomization

Subjects will be randomized after completing all screening procedures and satisfying the requirements of the study eligibility criteria. Randomization will be performed using a random permuted block design stratified by site and home dose (< 80 mg and ≥ 80 mg) with a 1:1 allocation ratio with Reprieve DMS as the treatment arm and ODT as the control arm.

Randomized treatment will be assigned from iMedNet. If, at any time after randomization, the subject becomes ineligible or withdraws, the subject is still considered randomized.

4.2 Blinding

The randomization schedule shall be blinded to the study subjects, site personnel and sponsor. The biostatistician and designates are privy to the randomization schedule.

After randomization, the study subjects, site personnel and sponsor will no longer be blinded to the treatment assignment.

4.3 Study Assessments

Refer to Table 1 of the CIP for the schedule of assessments.

5 Sample Size Determination

A maximum of 50 subjects will be randomized 1:1 to Reprieve DMS and ODT. This sample size is considered sufficient to provide conclude non-inferiority against the state-of-the-art HF therapy control. Based on current data from the FASTR- US study, and data from PUSH-AHF, a standard deviation for net sodium/24-hour loss of 250mmol/24 hours will be observed in both OTD and the Reprieve groups. The average sodium output in PUSH AHF sodium guided group was ~400 mmol/24 hours. The average sodium output in prior Reprieve studies has been >~500 mmol/24 hours. Based on these assumptions, with >100 mmol/24 hour observed greater sodium loss in the Reprieve group, 25 participants per group will have >90% power to conclude non-inferiority with a 140 mmol/24-hour margin.

6 Statistical Analyses

6.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted with widely accepted statistical or graphical software as required.

6.1.1 Descriptive Statistics

Continuous data will be summarized with the number of observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized with frequency counts and percentages.

All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Quartile, minimum and maximum values will be formatted with the same number of decimal places as the measured value.

Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

6.1.2 Study Day

Study Day 0 is defined as the initiation date of the randomized therapy. Day in study will be calculated relative to the initiation date of the randomized therapy as follows:

Study Day = Assessment Date – Initiation Date of Randomized Therapy

For each subject, duration in study will be based on the difference between the informed consent date and the last study contact date, which is the latest date of all follow-up visits, assessments, adverse events onset or resolution and study exit including date of death. Total duration in study will be calculated as follows:

Duration Days = Study Completion, Withdrawal or Death Date – Informed Consent Date

6.1.3 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

6.1.4 Statistical Significance

Unless otherwise specified, hypothesis testing will be performed at the two-sided 0.05 significance level. For the non-inferiority endpoint, a one-sided alpha of 0.025 will be utilized.

All probability values will be rounded to 4 decimal places. However, the number of digits to be displayed will depend on the parameter and result. All probability values that round to 0.0000 will be presented as “< 0.0001” and p-values that round to 1.0000 will be presented as “> 0.9999”. Two-sided probability values < 0.05 and one sided <0.025 values will be considered statistically significant.

6.2 Analysis Populations

The following populations will be considered for the analysis of data for this study:

1. Intent-to-Treat (ITT)

   The Intent-to-Treat population (ITT) will consist of all subjects who have undergone randomization.

   Subjects in the ITT population in whom the Reprieve Decongestion Management System was connected to the subject but not turned on will be followed through 30 days for safety purposes. These subjects will not be included in any efficacy endpoint analyses but will be included in a secondary safety analysis. Adverse events will be reported for all ITT subjects through 30 days. Subjects will be analyzed according to the treatment to which they were randomized.

2. As Treated (AT)

   Subjects will be included in the As Treated Population if they sign the ICF and the Reprieve Decongestion Management System is connected to the subject and turned on.

   The As Treated Population represents the Primary Safety Analysis Population for the study since all of these subjects will have received treatment with the DMS. However, if a subject is identified to not be responding to diuretic treatment after the initial two hours of administration of medication, the subject is deemed to need more aggressive treatment and is therefore withdrawn from the study.

3. Modified Intent-to-Treat (mITT)

   Subjects will be included in the Modified Intent-to-Treat Population if they sign the ICF and the Reprieve Decongestion Management System is connected to the subject, turned on and have undergone the diuretic ramp procedure.

4. Roll-Ins

   Each clinical site will have the opportunity to roll-in 2 subjects to be treated with the Reprieve DMS prior to randomization. All roll-in subjects will be analyzed separately from the other populations.

The primary efficacy and safety endpoints will be evaluated using the ITT, mITT and AT populations. Similarly, the secondary efficacy and safety endpoints and ancillary endpoints will be evaluated using the ITT, mITT and AT populations. All available data from the control group will be used for all efficacy and safety endpoints.

6.3 Handling of Missing Data

All attempts will be made to collect complete data for all subjects. Unless otherwise specified, no attempt will be made to impute missing data. Any missing study endpoint data will be described and will not contribute to the study endpoint analyses. The number of evaluable observations will be reported in the analysis.

In case of partial adverse event onset date or date of death, the unknown portion of the date of the event will be imputed.

In the case that the day portion is missing, the event will be assumed to have occurred on the 15th day of the given month and year, e.g. XX Mar 2022 -> 15 Mar 2022 where XX represents the unknown day.

In the case that the month and day are missing, the event will be assumed to have occurred on 30 June of the known year.

In the rare case that the event date is fully unknown, the date will be imputed as the initiation date of randomized therapy. Imputation of partial dates is subject to the condition that it must occur on or after the initiation date of randomized therapy. In the case where the imputed date is prior to the initiation date of randomized therapy, the date of the initiation date of randomized therapy will be used.

As death cannot occur before any documented subject contact, the imputed date of death must occur on or after last known contact in study.

6.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

6.5 Demographics and Baseline Characteristics

Tables of baseline characteristics, demographics and medical history will be summarized using descriptive statistics. For continuous measures, the number of observations, mean, median, quartiles, minimum and maximum will be reported for each measure. For categorical measures, the frequency counts and percentages for each category will be reported.

The proportion of subjects screened and enrolled will be tabulated.

6.6 Analysis of Study Endpoints

This section will discuss the tabulation and analysis of the study safety and efficacy. This study does not have a planned formal statistical analysis beyond analysis of the primary non-inferiority efficacy

endpoint. Descriptions of the statistical procedures that will be used to analyze the study endpoints will be described below.

6.6.1 Primary Safety Endpoint

The primary safety objective is to determine the safety of the Reprieve DMS to treat ADHF in patients admitted to the hospital or emergency department in comparison to control therapy without clinically significant acute kidney injury. The events will be assessed by an independent CEC.

The primary safety endpoint is defined as

- clinically significant acute kidney injury defined as KDIGO stage 2 or greater AKI (≥ doubling of baseline serum creatinine or use of renal replacement therapy (RRT)),
- severe electrolyte abnormality (serum potassium < 3.0 mEq/L, magnesium < 1.3 mEq/L or sodium < 125 mEq),
- symptomatic hypotension or
- hypertensive emergency.

The changes in creatinine and electrolytes will be evaluated from baseline to peak value during the maximum 72-hour study period after randomized therapy initiation. RRT includes hemodialysis, hemofiltration, hemodiafiltration, peritoneal dialysis and kidney transplant. Isolated ultrafiltration without dialysis will not be considered RRT. Hypertensive emergency is defined as blood pressure greater than 180/120 mmHg with end-organ damage. Symptomatic hypotension is defined as sustained hypotension (< 80 mmHg systolic) with corresponding symptoms that requires an intervention (i.e., fluid bolus or vasoactive medication).

The primary safety endpoint will be measured as a binary outcome with counts, percentages and 2-sided 95% Clopper-Pearson confidence intervals. The numerator will state the number of subjects experiencing a safety endpoint event and the denominator will state the number of total subjects. The safety endpoint will be analyzed using all available data. Subjects with missing safety endpoints will not be included with the analysis and will be described.

6.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is net sodium loss per 24 hours at end of randomized therapy.

The efficacy endpoint will be analyzed using all available data. Subjects with missing efficacy endpoints will not be included with the analysis and will be described.

A direct comparison between the two trial arms (man vs machine) will be made concerning the net urine sodium excretion during the duration of IV therapy normalized per 24 hours. This will be an ITT analysis,

but AT and mITT will also be reported. The primary effect parameter will be the mean difference in net sodium excretion with its 95% confidence interval. The mean difference will be estimated with linear regression. For non-inferiority, we will analyze whether the lower bound of the 95% CI crossed 140 mmol, our pre-specified non-inferiority margin. A p-value will also be presented.

6.6.3 Secondary Safety Endpoint

The secondary safety endpoint is all Device and Procedure related AEs and SAEs as determined by an independent CEC.

The following events will not be included as a secondary safety endpoint:

- Episodes of hematuria associated with Foley catheter placement that can be adequately managed as this is an anticipated event commonly associated with Foley placement.

The Device and Procedure related AEs and SAEs will be tabulated using counts and percentages.

6.6.4 Secondary Efficacy Endpoints

The first secondary efficacy endpoint is the net fluid loss per 24 hours at end of randomized therapy. The net fluid loss is calculated as the difference between total fluid output and total fluid input.

The second secondary efficacy endpoint is weight loss per 24 hours at end of randomized therapy. The weight loss is calculated as the difference between patient weight at the start and end of randomized therapy.

The third secondary efficacy endpoint is time on IV loop diuretic defined as the time from initiation of randomized therapy to last dose of IV loop diuretic administered for ADHF.

The fourth secondary efficacy endpoint is in hospital worsening renal function (≥ 0.3 mg/dL increase in serum creatinine) during randomized therapy.

The results for the four secondary efficacy endpoints will be presented using the mean, standard deviation, median, quartiles, minimum and maximum.

6.7 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately for each site using descriptive statistics.

Poolability of the primary efficacy endpoints across investigational sites will be evaluated using a regression model with fixed effects for treatment, site and treatment by site interaction. If one site

enrolls < 5 subjects will be dropped from the poolability analysis. If the p-value for interaction effect is < 0.15, additional exploratory analyses will be performed to understand any variation in outcomes by site.

Poolability of the primary safety endpoint across investigational sites will be evaluated using logistic regression model with a fixed effect for treatment, site and treatment by site interaction. If the p-value for the interaction effect < 0.15, additional exploratory analyses will be performed.

6.8 Safety Analyses

Adverse events (AE) will be reported for the mITT, ITT and AT populations based on the independent CEC adjudication. AEs will be tabulated with the number of events and subjects with event for each event type and overall. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval. Serious adverse events (SAE) will also be tabulated. The rate of all AEs and SAEs reported in the study will be reported.

Adverse events leading to death or study discontinuation will be provided in listing format. All device and procedure related events will be reported in listing format.

6.9 Subgroup Analyses

Not applicable.

6.10 Interim Analyses

No formal interim analyses will be conducted.

6.11 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by clinical sites on the CRF. Protocol deviations will be summarized for all deviations and by type with event counts and number of subjects with at least one deviation.

7 Changes from Planned Analyses

Not applicable.

8 Subject Listings

Subject listings will be provided for the primary efficacy and safety endpoints.

9 References

Shiang, K.D. (2004). "The SAS® Calculations of the Areas Under the Curve (AUC) for Multiple Metabolic Readings". https://www.lexjansen.com/wuss/2004/posters/c_post_the_sas_calculations_.pdf