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STATISTICAL ANALYSIS PLAN

Protocol Title (Number):
Evaluation of Fluid Volume in Patients with Sepsis and Refractory Hypotension
(FRESH Study)
PRO-0001

Sponsor: Cheetah Medical, Inc.

June 28, 2018

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1 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AKI	Acute Kidney Injury
[redacted]	[redacted]
CEC	Clinical Events Committee
CP_{sup}	Conditional Power to Claim Superiority
CRF	Case Report Forms
CSR	Clinical Study Report
DMC	Data Monitoring Committee
FDA	United States Food and Drug Administration
FRESH	Fluid Responsiveness Evaluation in Sepsis-associated Hypotension
ICU	Intensive Care Unit
IRB	Institutional Review Board
ITT	Intent-To-Treat Population
MITT	Modified Intent-To-Treat Population
PLR	Passive Leg Raise
PP	Per-Protocol Population
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SSR	Sample Size Re-estimation
SV	Stroke Volume
SVI	Stroke Volume Index
TEAE	Treatment Emergent Adverse Event

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2 SUMMARY

TITLE	Evaluation of fluid volume in patients with sepsis and refractory hypotension.
PREFACE	This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Cheetah Medical, Inc. protocol PRO-0001 *(Fluid Responsiveness Evaluation in Sepsis-associated Hypotension [FRESH] Fluid Trial)*. This study is being completed to assess the safety and efficacy in using Starling SV for dynamic assessment of fluid responsiveness in the treatment of septic patients with refractory hypotension. The following documents were reviewed in preparation of this SAP: • Clinical Research Protocol PRO-0001, issued 30OCT2017 • Case report forms (CRFs) issued 01DEC2017 for Protocol PRO-0001
PURPOSE	The purpose of this SAP is to outline the planned analyses in support of the Clinical Study Report (CSR) for protocol PRO-0001. Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR or manuscript.
STUDY OBJECTIVES	The objective of this study is to assess the mean difference in fluid balance at 72 hours or ICU discharge, whichever occurs first, and associated patient outcomes, based on a dynamic assessment of fluid responsiveness in septic patients with refractory hypotension in an ICU setting.
STUDY ENDPOINTS	**Primary:** Fluid balance (L) at 72 hours or ICU discharge, whichever occurs first **Secondary:** 1. Changes in serum creatinine level from baseline to 72 hours (key secondary endpoint) 2. Requirement for renal replacement therapy (RRT) 3. Requirement for ventilator use 4. Length of ICU stay (days) until subject is medically ready for discharge 5. Number of hours with ventilator use (30-day period) 6. Number of hours with vasopressor use **Not for Formal Testing:** 1. Incidence of Adverse Events (AE) 2. Number of ICU readmissions 3. 30 day in-hospital Mortality rate 4. Volume of Treatment Fluid 5. Incidence of MACE 6. Discharge location 7. Mean difference in fluid balance at ICU discharge
STUDY DESIGN	This study is a prospective, multi-center, randomized trial comparing the mean difference in fluid balance and associated patient outcomes between a treatment guided by a dynamic assessment of fluid responsiveness and a standard of care control group not using dynamic fluid assessment.

	Subjects will be randomized in a 2:1 treatment to control group ratio to increase power for sub-analysis by patient population. Subject randomization will be stratified by time window of enrollment to ensure even randomization between the three time windows of enrollment (0-6 hours, 6-12 hours, and 12-24 hours). Patients randomized to the Starling SV arm will have treatment guided by a dynamic assessment of fluid responsiveness (measured by a change in stroke volume index > 10%) as assessed by passive leg raise (PLR). Patients randomized to the control group will receive standard of care treatment. The use of dynamic fluid assessment (i.e. SVV, PPV, or SV change) to determine fluid responsiveness within the control group is prohibited.
INTERIM ANALYSES	An interim analysis is planned after 90 subjects have been enrolled and completed the evaluation of the key secondary endpoint of change in serum creatinine at 72 hours. At this analysis, a sample size re-estimation will occur in order to determine promise for superiority in the key secondary endpoint. No annual reports for the FDA are anticipated prior to the end of data collection as this study is not intended to support a regulatory filing. An annual report and project status update may be requested by the local IRB at study sites. No other interim analyses are planned.
FINAL ANALYSES	All final planned analyses identified in this SAP will be completed after the last subject has completed their 30 day follow up.

3 SEQUENCE OF PLANNED ANALYSES

3.1 INTERIM ANALYSES

3.1.1 INTERIM ANALYSES FOR SAMPLE SIZE OF SECONDARY ENDPOINT SUPERIORITY

The trial will incorporate a sample size re-estimation (SSR) at the time of the interim look based on promise for superiority in the key secondary endpoint of change in serum creatinine from baseline to 72 hours. The maximum enrollment being considered for this trial is 210 total enrolled (N_{max} = 1.75 times N_{min} = 120, where the sample size of 120 is determined as noted in Section 5 below).

The interim analysis on the key secondary endpoint incorporating a SSR will take place when 90 subjects have been enrolled and completed the key secondary endpoint evaluation. The interim analysis will be performed by an independent statistician. It is assumed that the acute endpoint assessments will be fully informed at the time of the interim analysis.

There will be no inspection of the primary study endpoint at this interim stage. The primary study endpoint will be tested as final at the formal planned final sample size of 120 patients and will not incorporate an alpha spent. In the event of an SSR due to the key secondary endpoint, the primary endpoint will be tested again at the final sample size. No alpha-adjustment is needed across this potential multiple testing of the primary endpoint since the primary endpoint will need to be met at <u>both</u> N_{min}=120 and, if the sample size is increased to >120, at the final sample size.

After 90 patients have completed the secondary endpoint, the conditional power to claim superiority (CP_{sup}) on the key secondary endpoint for change in creatinine level from baseline to 72 hours will be computed assuming a planned final sample size of 120 patients. The conditional power (CP_{sup}) will be calculated based on the observed interim results of the key secondary endpoint, with the specific interest of demonstrating superiority of the experimental treatment versus the control. The data will be partitioned into three zones based on CP_{sup} unfavorable zone (CP_{sup}<50%), promising zone (50%≤CP_{sup}<80%), and favorable zone (CP_{sup}≥80%). If CP_{sup}<50% or CP_{sup}≥80% the study will continue as is. If 50%≤CP_{sup}<80% then the sample size may be increased (to a maximum of 210 total) to yield 80% CP_{sup} without increasing Type I error, following the methodology of Chen, DeMets and Lan (2004).

3.1.2 ANNUAL REPORTS

As this study is not designed to support regulatory filings, no annual reports are anticipated at this time. Annual project updates may be provided at the request of site IRBs.

3.2 Final Analyses and Reporting

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last subject has had 30-day follow-up. Key statistics and study results will be made available to Cheetah Medical, Inc. following database lock. Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported as necessary. Any results from these unplanned analyses will also be clearly identified as post-hoc analyses.

4 Study Objectives and Endpoints

4.1 Study Objective

The objective of this study is to assess the mean difference in fluid balance at 72 hours or ICU discharge, whichever occurs first, and associated patient outcomes, based on a dynamic assessment of fluid responsiveness in septic patients with refractory hypotension in an ICU setting.

4.2 Study Endpoints

4.2.1 Primary Endpoint Analysis

The primary endpoint analysis is an evaluation of the difference (L) between the two treatment groups' mean fluid balance at 72 hours or ICU discharge, whichever occurs first. The following are the null and alternative hypotheses:

$$H_0: \mu_c - \mu_t = 0$$
$$Ha: \mu_c - \mu_t \neq 0$$

where μ_t and μ_c are the average fluid balance in the Starling SV and control groups, respectively.

4.2.2 Secondary Endpoints

4.2.2.1 For formal testing

Key secondary endpoints for the purposes of formal statistical testing are:

- Changes in serum creatinine level from baseline to 72 hours (key secondary endpoint)
- Requirement for renal replacement therapy (RRT)
- Requirement for ventilator use
- Length of ICU stay (days) until subject is medically ready for discharge
- Number of hours with ventilator use (30-day period)
- Number of hours with vasopressor use

4.2.2.2 Not for formal testing

Additional exploratory secondary endpoints identified for testing, but will not be included in the formal statistical testing procedures for key secondary endpoints are:

- Incidence of Adverse Events (AE)
- Number of ICU readmissions
- Mortality rate
- Volume of treatment fluid
- Incidence of Major Adverse Cardiac Event (MACE)
- Discharge location
- Mean difference in fluid balance at ICU discharge

5 SAMPLE SIZE

Subjects will be randomly assigned in a 2:1 ratio to treatment with Starling SV or to treatment with standard of care, stratified by time window of enrollment (0-6 hours, 6-12 hours, and 12-24 hours). The primary effectiveness endpoint for this study is fluid balance at ICU discharge.

Minimum enrollment (N_{min}) in the study will be set at 120 subjects (80 Starling SV and 40 control) to power at 80% for demonstration of superiority of means for the secondary endpoint of creatinine levels as a measurement of change from baseline at 72 hours. The secondary endpoint for change in creatinine levels at 120 evaluable subjects displays 80% power at a two-sided alpha level of 0.05 to demonstrate superiority of Starling SV under an assumption of an average treatment effect of -1.4 mg/dL with a standard deviation of 2.5 mg/dL.

Under an assumption of an average treatment effect of -2 L with a standard deviation of 3 L, the sample size of 120 evaluable subjects provides 92.7% power in a test of superiority of means for the primary effectiveness endpoint at a two-sided 0.05 level of significance.

The trial will incorporate a sample size re-estimation (SSR) at the time of the interim look (after 90 patients have been evaluated for the key secondary endpoint) based on promise for superiority in the key secondary endpoint. Sample size re-estimation, described in further detail in Section 3.1, will result in a maximum of 210 total evaluable subjects, or no more than 1.75 times the minimum of 120.

6 Analysis Populations

6.1 All Enrolled

Any subject who has signed informed consent will be included in the all enrolled population. Should a subject be considered a screen failure, the reason for failure will be documented and the subject will be exited from the study.

6.2 Intent to Treat Population (ITT)

The intent-to-treat (ITT) population for this study includes subjects that are enrolled in the study, have signed the ICF, meet study eligibility criteria, and have been randomized to either the treatment or control arm of the study.

6.3 Modified Intent to Treat Population (mITT)

Subjects will be included in the Modified Intent-to-Treat (mITT) group if they sign the ICF, meet study eligibility criteria, are randomized, and in the treatment group receive monitoring for the first 72 hours of study enrollment or until ICU discharge, whichever occurs first. The mITT population will be conducted as a supportive analysis population for the primary and secondary endpoints.

6.4 Per-Protocol (PP)

Subjects will be included in the Per-protocol group if they sign the ICF, are randomized and have the assigned procedure completed, meet critical study eligibility criteria and have no major protocol deviations (to be pre-defined as an attachment to the interim and final analyses), and, in the treatment group, receive monitoring for the first 72 hours of study enrollment. The PP population represents the primary analysis population for the primary and secondary endpoints.

6.5 Safety

Subject will be included in the safety group if they are in the ITT analysis population and study treatment was at least attempted. This is the primary analysis population for safety, including adverse events (this is a change from the protocol, where it states that adverse events will be reported on all enrolled patients; it has been since felt that this could underreport the true adverse event rates in patients to whom randomized treatment was attempted). Patients are analyzed under the treatment received.

7 General Issues for Statistical Analysis

7.1 Analysis Software

Analysis data sets, statistical analyses and associated output generated by [redacted] will be generated using SAS® Software version 9.4 or later or R version

3.2.3 or later. [redacted] Standard Operating Procedures (SOPs) will be followed in the creation and validation of all analysis datasets, tables, listings, figures and analyses.

7.2 Disposition of Subjects and Withdrawals

All subjects who provide written informed consent will be accounted for. The number and percent of subjects in each analysis population will be presented, where the percentage is based on the number of enrolled subjects. The number and percent of PP, mITT and ITT subjects who completed each scheduled assessment will be presented. The frequency and percent of PP, mITT and ITT subjects randomized at each investigational site by treatment arm will be presented. A flow chart and listing will also summarize subject accountability.

The number and percentage of subjects prematurely withdrawing from the study will be presented all enrolled subjects by treatment group overall and by reason for premature withdrawal. Descriptive statistics (mean, standard deviation, median, minimum, maximum) of number of days on study will be presented by treatment group.

7.3 Methods for Withdrawals, Missing Data, and Outliers

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to death, loss to follow-up, withdrawal, non-adherence to the protocol, and possible non-evaluable assessments. Since this is unlikely due to the short follow-up time schedule and the consistent nature of data collection, missing data will not be imputed. However, should more than 5% of subjects be missing evaluable data for the primary endpoint, then as a sensitivity analysis to assess the impact of missing data on the primary endpoint treatment comparisons, treatment group comparisons on the primary endpoint will be performed where missing data are first imputed via multiple imputation linear regression using the FCS method in SAS. The multiple imputation model will use, as covariates in the imputation model, the demographic variables shown in the demographics table shell in Appendix A. A total of 10 complete datasets will be created for the multiple imputation and the primary endpoint treatment comparisons will be carried out within each imputed dataset; results will then be combined across imputed datasets using standard multiple imputation techniques in PROC MIANALYZE to obtain one treatment comparison p-value on the primary endpoint. Tables detailing missing data and analysis populations will be provided in the final report. Should the sensitivity analysis be required, it will also be provided in the final report.

7.4 Protocol Violations

A protocol violation is a failure to comply with the requirements specified within this clinical study protocol. Protocol violations will be summarized in the CSR. This summary will include the number and percent of subjects (overall and by site) with each violation type for the ITT analysis set. Protocol violations, according to section 14.2 of the protocol and the Protocol Deviation CRF, include:

- Failure to obtain subject's informed consent prior to any study-related activities;
- Subject did not meet the inclusion and/or exclusion criteria and were enrolled;
- Failure to conduct protocol required clinical test or assessment;
- Failure to complete protocol required assessments within the required time frame
- Failure to perform assessment or test according to the protocol
- Failure to report serious adverse events according to protocol requirements.

7.5 Multiple Comparisons and Multiplicity

It is recognized that with a multiplicity of tests comes inflation in the chance of a false finding. Therefore, formal statistical testing will only be done for the following secondary endpoints:

- Changes in serum creatinine level from baseline to 72 hours (key secondary endpoint)
- Requirement for renal replacement therapy (RRT)
- Requirement for ventilator use
- Length of ICU stay (days) until subject is medically ready for discharge
- Number of hours with ventilator use (30-day period)
- Number of hours with vasopressor use

These endpoints will be tested in a hierarchical (sequential) manner in the order given above (and testing will only proceed if a significant beneficial treatment effect is detected in the primary endpoint). Specifically, the first secondary endpoint (change in creatinine) will be compared between treatments at a two-sided 0.05 level of significance. If significant in the direction favoring Starling SV, then Starling SV will be considered beneficial on change in serum creatinine level, and the next endpoint (ICU stay) will be compared between treatments at a two-sided 0.05 level of significance; otherwise the statistical testing will stop and Starling SV will not be considered statistically significantly beneficial on any secondary endpoint. If the treatment comparison is able to proceed to this next secondary endpoint of ICU stay, it will be carried out at the two-sided 0.05 level of significance. If the treatment comparison is significant in the direction favoring Starling SV, then Starling SV will be considered beneficial on this endpoint and testing will proceed in a similar manner for the remaining endpoints; otherwise, treatment comparisons will stop and Starling SV will not be considered beneficial on this second secondary endpoint of ICU stay nor on all endpoints after it in the above sequence.

7.6 Assessment of Homogeneity

To evaluate difference among sites in the study, summaries of baseline variables and endpoints by site will be tabulated for the PP analysis set. Comparisons will be made across sites for selected baseline variables. Continuous baseline data will be compared across sites for the PP analysis set using one-way ANOVA; categorical data will be compared across sites using the chi-square test.

To assess consistency in the treatment effect on the primary endpoint and on continuous secondary endpoints across sites, two-way ANOVAs with the main effects of treatment group and site and with the treatment group by site interaction effect will be carried out on the PP and mITT analysis sets. An endpoint with an interaction effect that is not significant at the 0.15 level of significance will be considered as supporting the poolability of data across sites for the treatment comparisons on that endpoint. Otherwise, treatment comparisons within sites will be inspected to determine the direction and magnitude of the interaction; if treatment effect is consistent in direction across sites centers but only differs in magnitude across sites, poolability of sites for the endpoint analysis is also supported. Any site with fewer than six subjects (combined treatment and control) will be combined into a single pooled site for purposes of this analysis.

The above assessment of consistency will be repeated across the following subgroups, with appropriate descriptive statistics being presented for each treatment group within each subgroup category:

- Patient disease state
- Patients determined to be fluid responsive vs non-fluid responsive
- AKI measures in patients determined to increase serum creatinine levels from baseline vs decrease serum creatinine levels from baseline (AKI measures vs. no AKI measures)
- Enrollment time frame (0-6 hours, 6-12 hours, 12-24 hours)
- Sex

Dichotomous secondary endpoint data will similarly be analyzed for poolability using logistic regression analysis.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

8.1 DEMOGRAPHICS

Demographics will be summarized by treatment group for the PP and mITT analysis sets. There will be no formal statistical comparisons between treatment groups on demographic variables. The continuous variables of age, height (cm), weight (kg), BMI, qSOFA, SOFA, FiO_2, and Glascow Coma Score will be summarized by treatment group using sample size, mean, standard deviation, minimum and maximum. For the categorical variables of sex (male, female), race (white, black or African American, American Indian/Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, other, unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown), known or presumed infection, SIRS criteria exhibited (Temperature >38 C, Temperature <36 C, Heart Rate > 90/min, Respiratory rate >20/min or PaCO2 <32mm, White Blood Cell Count >12000/mm3, White Blood Cell Count <4000/mm^3,White Blood Cell Count

>10% Immature Cells), smoking history (never, current, former), sepsis diagnosis (bacterial, fungal, viral, parasitic, other), Receiving Respiratory Support, and Cardiovascular Score (MAP ≥ 70 mmHg, MAP < 70 mmHg, Dopamine <5 or dobutamine (any dose), Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1, Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1), the number and percentage of patients in each category will be presented for each treatment group.

8.2 Prior and Concurrent Medications

A listing will be provided detailing subjects' medications, but no table is planned at this time.

8.3 Baseline Medical History

The medical history of all PP and mITT subjects will be summarized in a table by treatment group. For each condition, the number and percent of subjects who currently have the condition, who have a resolved history of the condition, and who have no prior history will be presented. The list of conditions is captured in the FRESH Medical History CRF.

8.4 Baseline Labs and Vital signs

A table presenting descriptive statistics (sample size, mean, standard deviation, median, min and max) of laboratory variables and vital signs by treatment group at baseline will be provided for the PP and mITT analysis sets. The laboratory variables are hemoglobin, serum creatinine, lactate levels, platelets, and bilirubin, and the arterial gases pH, $PaCO_2$, PaO_2, HCO_3, O_2CT, and O_2SAT. The vital signs are body temperature (C), heart rate (bpm), respiration rate (breaths/min), pulse oximetry (%), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg).

9 Efficacy Analyses

All efficacy analyses will be performed on the PP analysis population (primary) and mITT analysis population (supportive).

9.1 Primary Efficacy Variable

The primary endpoint analysis is an evaluation of the difference between the two treatment groups in mean fluid balance (L) at 72 hours or ICU discharge, whichever occurs first. The following hypothesis will be tested:

$$H_o: \mu_c - \mu_t = 0$$
$$Ha: \mu_c - \mu_t \neq 0$$

where μ_t and μ_c is the average fluid balance in the Starling SV and control groups, respectively. Statistical summaries will include means, medians, quartiles and standard deviation for each

treatment group, as well as 95% confidence interval of the difference between treatment group means. Subjects that enter the study on dialysis, or are on chronic dialysis, are excluded from this endpoint. A two-sample t-test will be used to test the null hypothesis at a two-sided 0.05 level of significance. A significant p-value combined with a lower sample mean for Starling SV than for the control group will indicate statistical superiority of Starling SV over the control with respect to the primary endpoint. Fluid balance will be analyzed under sensitivity analyses not intended for formal hypotheses testing.

9.2 Secondary Efficacy Variables

9.2.1 For Formal Testing Using the Sequential Approach

If a significant beneficial Starling SV effect is found in the primary endpoint, the following secondary endpoints will be compared between treatments in the sequential manner discussed above.

9.2.1.1 Changes in Serum Creatinine Levels from Baseline to 72 hours or ICU discharge

The hypotheses of interest relating to the mean change in serum creatinine level from baseline to 72 hours or ICU discharge, whichever comes first, are as follows:

$$H_0: \mu_t = \mu_c$$
$$H_1: \mu_t \neq \mu_c$$

where μ_t and μ_c represent the mean change in serum creatinine level from baseline to 72 hours in the treatment and control groups, respectively. The treatment groups will be compared with respect to the mean days using an analysis of covariance adjusting for baseline serum creatinine. Subjects that enter the study on dialysis are excluded from this endpoint. Subjects that are put on dialysis within 72 hours, or prior to ICU discharge, will have the final creatinine value prior to dialysis used for the change from baseline calculation. All creatinine values post dialysis treatment are not applicable to this endpoint test. Summary of this endpoint will include the mean, median, quartiles, minimum, maximum and standard deviation of levels for each treatment arm, a 95% confidence interval for the difference in the two treatment arm mean levels, and the p-value from the test described above.

9.2.1.2 Requirement for Renal Replacement Therapy (RRT)

The hypotheses of interest relating to RRT are as follows:

$$H_0: P_t = \mathrm{P}_c$$
$$H_1: P_t \neq \mathrm{P}_c$$

where P_t and P_c represent the proportion of subjects requiring RRT in the treatment and control groups, respectively. Treatments will be compared using the chi-square test. Subjects that enter the study on dialysis, or are on chronic dialysis, are excluded from this endpoint. Summary of this endpoint will include the number and percentage of patients requiring RRT, a 95% confidence interval for the risk difference in the two arm percentages calculated using the normal

approximation to the binomial distribution, and the p-value from the test described above. If the observed event rates are less than 10% in either treatment group, a Fisher's exact test will be used to compare treatments instead of the chi-square test, and the 95% confidence of the risk difference will be based on the Wilson method instead of the normal approximation to the binomial distribution.

9.2.1.3 Requirement for Ventilator Use

The hypotheses of interest relating to ventilator use are as follows:

$$H_0: P_t = P_c$$
$$H_1: P_t \neq P_c$$

where P_t and P_c represent the proportion of subjects requiring ventilator use in the treatment and control groups, respectively. Treatments will be compared using the chi-square test. Subjects that enter the study on ventilation are excluded from this endpoint analysis. Summary of this endpoint will include the number and percentage of patients requiring ventilator use, a 95% confidence interval for the risk difference in the two arm percentages calculated using the normal approximation to the binomial distribution, and the p-value from the test described above. If the observed event rates are less than 10% in either treatment group, a Fisher's exact test will be used to compare treatments instead of the chi-square test, and the 95% confidence of the risk difference will be based on the Wilson method instead of the normal approximation to the binomial distribution.

9.2.1.4 Length of ICU Stay

The distribution of treatments with respect to length of ICU stay (days) will be compared between treatments using the Wilcoxon Rank Sum test given the expected skewness in this variable. Subjects that die while in the ICU will be censored from the analysis. ICU length of stay will be calculated using the earliest of date that the subject is medically ready for discharge when captured, the date of discharge, or the study exit date.

Summary of this endpoint will include the mean, median, quartiles, minimum, maximum and standard deviation of days for each treatment arm, a 95% confidence interval for the difference in the two treatment arm mean days, and the p-value from Wilcoxon Rank Sum test.

9.2.1.5 Number of Hours with Ventilator Use

The hypotheses of interest relating to the number of hours free from ventilator use (within 30 days) are as follows:

$$H_0: \mu_t = \mu_c$$
$$H_1: \mu_t \neq \mu_c$$

where μ_t and μ_c represent the mean number of hours in the treatment and control groups, respectively. The treatment groups will be compared with respect to the mean hours using a two-

sided two-sample t-test. Subjects that enter the study on ventilation are excluded from this endpoint analysis. Summary of this endpoint will include the mean, quartiles, median, minimum, maximum and standard deviation of hours for each treatment arm, a 95% confidence interval for the difference in the two treatment arm mean hours, and the p-value from the test described above.

9.2.1.6 Number of Hours with Vasopressor Use

The hypotheses of interest relating to the number of hours with vasopressor use are as follows:

$$H_0: \mu_t = \mu_c$$
$$H_1: \mu_t \neq \mu_c$$

where μ_t and μ_c represent the mean number of hours in the ICU in the treatment and control groups, respectively. The treatment groups will be compared with respect to the mean hours using a two-sided two-sample t-test. Summary of this endpoint will include the mean, median, quartiles, minimum, maximum and standard deviation of hours for each treatment arm, a 95% confidence interval for the difference in the two treatment arm mean hours, and the p-value from the test described above.

9.2.2 NOT FOR FORMAL TESTING

9.2.2.1 Incidence of Treatment Emergent Adverse Events (AE)

A Treatment Emergent Adverse Event (TEAE) is one that started or worsened in severity during or after randomized treatment was attempted. The number and percentage of patients with incidence of at least one TEAE will be summarized by treatment arm in a table. The summary will include the number and percent of subjects experiencing one or more AEs cumulatively up to 72 hours, one week, and 30 days. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in rates between the two arms at each time point will be completed and included using the normal approximation to the binomial distribution.

The analysis will be repeated for serious TEAS. In addition, the number and percentage of patients with at least one TEAEs will be presented by severity and relationship to study procedure; patients with more than one TEAE will be categorized according to the maximum severity and maximum relationship experienced.

9.2.2.2 Number of ICU Readmissions

The number of ICU readmissions through 30 days will be summarized by treatment arm in a table. The summary will include the number and percent of subjects with 0, 1, or >1 ICU readmissions. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in rates between the two arms will be completed and included using the normal approximation to the binomial distribution or Wilson method (if an observed rate is less than 10% in any treatment group).

9.2.2.3 Mortality Rate

The mortality rate will be summarized by treatment arm in a table. The summary will include the number and percent of subjects who died by arm; Kaplan-Meier mortality curves will be presented for each treatment group. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in rates between the two arms will be completed and included using the normal approximation to the binomial distribution or Wilson method (if an observed rate is less than 10% in any treatment group).

9.2.2.4 Volume of Treatment Fluid

The volume of treatment fluid will be summarized by treatment arm in a table. The summary will include the mean, standard deviation, median, minimum and maximum by arm. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in means between the two arms will be completed and included.

9.2.2.5 Incidence of Major Adverse Cardiac Event (MACE)

The incidence of MACE through to 72 hours, one week, and 30 days will be summarized by treatment arm in a table. The summary will include the number and percent of subjects by arm by category. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in rates between the two arms will be completed and included using the normal approximation to the binomial distribution or Wilson method (if an observed rate is less than 10% in any treatment group). Kaplan-Meier curves of time to first component of MACE will be presented by treatment group.

9.2.2.6 Discharge Location

The discharge location will be summarized by treatment arm in a table. The summary will include the number and percent of subjects by arm by category. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in rates between the two arms will be completed and included using the normal approximation to the binomial distribution or Wilson method (if an observed rate is less than 10% in any treatment group).

9.2.2.7 Fluid Balance at ICU discharge

The fluid balance at ICU discharge will be summarized by treatment arm in a table. The summary will include the mean, standard deviation, median, quartiles, minimum and maximum by arm. Though no formal hypothesis tests are planned, 95% confidence intervals for the difference in means between the two arms will be completed and included.

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10 ADVERSE EVENTS

All adverse events (AEs) will be coded using the standardized Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version 19.1 or greater. Adverse event analyses will be performed on the mITT and Safety analysis populations.

10.1 ALL TREATMENT EMERGENT ADVERSE EVENTS

The number of TEAEs and the number and percentage of patients with at least one TEAE, with at least one device-related TEAE, with at least one serious TEAE and with at least one device-related TEAE will be presented by treatment group. These summaries will be presented for TEAEs occurring from start of treatment through 72 hours, from 72 hours through Discharge, from Discharge through 30 days, and from the start of treatment through 30 days.

The number of TEAEs and the number and percentage of patients with at least one TEAE will be presented for each treatment group by MedDRA system organ class and preferred term. This analysis will be repeated for serious TEAEs (collected through 72 hours only), device-related TEAEs, and AEs leading to withdrawal from the study.

In addition, the by-treatment number and percentage of patients with at least one TEAEs will be presented by severity and relationship to study procedure within each system organ class and preferred term; patients with more than one TEAE within a given system organ class and preferred term will be categorized according to the maximum severity and maximum relationship experienced.

A listing of all adverse events will include the subject number, AE number, days since index procedure, the AE SOC and PT, the severity of AE, whether the AE is classified as serious (SAE), the relationship of the AE to the investigational device or procedure, the action taken, the outcome, and the adjudication status.

10.2 LABORATORY VALUES AND VITAL SIGNS

Descriptive statistics of each laboratory value and vital sign and of the change from baseline for each will be presented at each post-baseline visit at which they are measured. Descriptive statistics to be presented are mean, standard deviation, median, minimum, and maximum.

10.3 DEATHS

In addition to the secondary endpoint analysis, should any subjects die during the FRESH study, relevant information will be supplied in a data listing.

11 Reporting Conventions

All reporting will meet the standards of [redacted] SOP BS002 and its associated work instructions.