Document Coversheet

Study Title: Repeated Amiodarone Dosing In Cardiac surgicaL Procedures

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1. STATISTICAL ANALYSIS PLAN

Because the effect size of the RBDR (Repeated Bolus Dosing Regimen) regimen is unknown, a sample size calculation was not completed. After all research procedures have been completed for 60 subjects (30 subjects in each treatment group) that have been randomized, the primary outcome analysis will be performed as described below. If there is a clinically-significant and a statistically-significant finding in the primary outcome analysis, defined as a p-value <0.05, the study will be closed and all statistical analyses described below will be completed. If there is a clinically-significant but not statistically significant finding in the primary outcome analysis, defined as a p-value between 0.05 and 0.10, the study will be extended to randomize another 20 subjects. Following the recruitment of these additional 20 subjects, the study will be closed and all statistical analyses described below will be completed. If there is neither a clinically-significant or statisticially-significant finding in the primary outcome analysis, defined as a p-value > 0.10, the study will be closed and all statistical analyses described below will be completed.

1.1 Baseline and demographic data

To describe baseline and demographic data, preoperative, intraoperative and postoperative data will be summarized and compared between patients randomized to the CDR (Conventional Dosing Regimen) and RBDR groups. Binomial and categorical data will be described as number (N) and percentage. Continuous data will be analyzed for normality. Data will be tested for normality using the Shapiro-Wilk test. Normal data will be described by the mean and standard deviation; whereas, non-normal data will be described by the median and interquartile range. Nominal data will be compared with the Fischer's Exact test or the Chi-Square test, as

appropriate. Normal continuous data will be compared with the 2-tailed, student t-test. Non-normal continuous data will be compared with the Mann-Whitney U test. All results with $p<0.05$ will be considered significant.

1.2 Primary Objective

To assess the primary objective, the number and percentage of patients in each group who have converted to NSR after 24 hours will be calculated. The number of patients who convert to NSR in each group will be compared with either the Fischer's Exact test or the Chi-Square test, as appropriate.

1.3 Secondary Objectives

To assess the secondary objectives, the following statistical analysis plan will be used:

- To compare the total time, in minutes, during the first 24 hours that the patient achieves target HR (HR < 110) between groups, first, the time that each patient has the target HR will be calculated. The total time at target HR will be calculated as the number of hourly HR measures ≤ 100 x 60 minutes. This calculated time data for each group will be will be analyzed for normality. Normal data will be described by the mean and standard deviation; whereas, non-normal data will be described by the median and interquartile range. If one group is normal and one group is non-normal, both groups will be reported as non-normal data. The total time at target HR between groups will then compared with either the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the time to achieve target HR (HR ≤ 110 bpm) between patients in each group, the time to achieve target HR will be calculated for each patient. This time will be calculated as the total time, in minutes, between the start of the initial amiodarone bolus and the first recorded HR ≤ 110 bpm. The time to achieve NSR data will be analyzed for normality. Normal data will be described by the mean and standard deviation, whereas non-normal data will be described by the median and interquartile range. If one group is normal and one group is non-normal, both groups will be reported as non-normal data. The time to achieve NSR will then compared with either the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the time to achieve NSR between patients in each group, the time to achieve NSR will be calculated for each patient. For patients who do not convert to NSR by the time they are discharged from the hospital, the date/time that they achieve NSR will be the date/time of hospital discharge. The time to achieve NSR data will be analyzed for normality. Normal data will be described by the mean and standard deviation, whereas non-normal data will be described by the median and interquartile range. If one group is normal and one group is non-normal, both groups will be reported as non-normal data. The time to achieve NSR will then compared with either the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the percentage of patients who achieve NSR by ICU discharge and hospital discharge, the number of patients in each group who have converted to NSR at each time point will be calculated and reported as number and percentage. The number who have

achieved NSR will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate.

- To compare the percentage of patients who have recurrent AF before ICU discharge and hospital discharge, the number of AF episodes after the initial AF episode will be counted for each patient in each group prior to ICU discharge and prior to hospital discharge. The mean (normal data) or median (non-normal data) number of additional AF episodes will be compared between the groups using the 2-tailed, independent samples student t-test (normal data) or with the Mann-Whitney U test (non-normal data).

- To compare the incidence and severity of hypotension, the number of patients who develop hypotension will first be calculated and reported as number and percentage. The number of patients with hypotension will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate . The number of patients who develop mild, moderate, severe or very severe hypotension will then be calculated and reported as number and percentage. The number of patients with each severity class will then be compared between groups using Somers' D test for ordinal data.

- To compare the incidence and severity of conduction abnormalities, the number of patients who develop bradycardia will first be calculated and reported as number and percentage. The number of patients with bradycardia will be compared with the Fischer's Exact test or the Chi-Square test, as appropriate. The number of patients who develop mild, moderate, severe or very severe conduction abnormalities will then be calculated

and reported as number and percentage. The number of patients with each severity class will then be compared between groups using Somers' D test for ordinal data.

1.4 Exploratory Objectives

- To evaluate preoperative, intraoperative and postoperative factors that affect the efficacy of the amiodarone dosing strategy in achieving NSR at 24 hours, ICU discharge and hospital discharge, multiple variable logistic regression modeling will be constructed using any significant variable discovered in the bivariate analysis.
- Evaluate preoperative, intraoperative and postoperative factors that affects the safety profile of the repeated amiodarone bolus dosing regimen, multiple variable logistic regression modeling will be constructed using any significant variable discovered in the bivariate analysis.