

Supplementary Table

Reason for Missing Month 3 LVEF Assessment

N=248 Patients

Died prior to month 3 visit: 85

Withdrew from study due to non-fatal adverse event: 65

Withdrew from study due to loss to follow-up: 4

Withdrew from study due to cardiac transplant: 5

Withdrew from study due to personal/administrative reasons: 41

Withdrew from study due to other reasons: 18

Attended visit but LVEF not recorded: 4

Missed visit but continued in study: 26

Methodology Supplement

Cox Modeling with Change in LVEF as a Time-Dependent Covariate

For the Cox model to employ the measurement of LVEF as a time-dependent covariate, a value for LVEF had to be available at each event time. This required the construction of a new analysis dataset containing the three protocol-specified LVEF results for all 2708 patients. The first step was to estimate LVEF at study day 90 for subjects with month 3 data available and to estimate LVEF at study day 365 for patients with month 3 and 12 visit values available. This was performed using linear interpolation or linear extrapolation depending on the actual visit dates occurring before or after the target study days of 90 and 365. The second step replaced missing study day 90 and 365 values with multiple imputation via SAS® procedure MI. Two stages were employed, with missing Day 90 LVEF first being imputed using baseline covariates and the existing Day 90 values as predictors. Missing Day 365 data were then imputed using the same baseline covariates as in the first stage, plus the Day 90 values (either actual or imputed), and non-missing Day 365 values as predictors. The predictors consisted of the 15 baseline covariates that were eligible for the stepwise model building process for each endpoint described earlier. Each imputation was run five times within each stage and performed separately for the patients of each treatment. For a given Cox model, the 5 imputed datasets provided 5 sets of estimates of log hazard ratios for the various predictors, including the time-dependent LVEF predictor, and their standard errors. These were combined via SAS® procedure MIANALYZE to derive a single log hazard ratio and confidence limits for each parameter of each model.