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Proposed Post-Approval Study

1.0 Overview

As requested by FDA, the major features of the proposed post-market registry are as follows:

- **Target Population:** patients implanted with the OPTIMIZER SMART System in the US following PMA approval
- **Patient enrollment period:** a minimum of 3 years
- **Minimum # of Patients enrolled:** 300
- **Patient follow-up duration:** a minimum of 2 years
- **Data Collection**
    - Data collection variables and format will be similar to that of the approved LAAO and TAVR Registries
    - Data collected will encompass the following categories:
        - Demographics and History
        - Baseline and Physical Assessments
        - OPTIMIZER Implantation Details
        - Acute (Procedural) Safety
        - Chronic Safety (Mortality, Serious Device or Procedure Related Adverse Events)
        - Prognostic data required for SHFM Score
        - Follow-Up (every 12 months)

- **Safety Oversight:**
    - An independent DSMB will monitor safety data, including review of the mortality data as compared to the SHFM prognostic score, and make recommendations to sponsor on safety of continued enrollment into the registry
    - IRB review at each participating center
    - **Technology solutions** (remote monitoring) will be sought to simplify/automate follow up wherever possible

2.0 Statistical Analyses

The OPTIMIZER has shown in multiple trials improvement of exercise tolerance, quality of life and functional status and reductions in HF hospitalizations. Accordingly, the post marketing study will focus on additional evidence on mortality. Statistical analyses for the post-market registry are also under discussion with FDA at this time, however, we expect the analysis to be as follows.

1. All-cause mortality based on vital checks
2. 1 and 2 year mortality assessment as compared to the SHFM prognostic scoring system
3. Kaplan-Meier survival

Kaplan-Meier curves will be constructed to examine (i) the time-dependent proportion of patients surviving. This rate will be reviewed periodically by the DSMB. In addition, we will use the method described in Kuschyk et al. to compare the observed survival to that predicted for a demographically and medically similar patient population using the SHFM mortality model. Briefly, the observed Kaplan-Meier curve with its associated 95% confidence bands will be compared to survival predicted from the prognostic model. The DSMB will assess whether there is a statistically or clinically significant deviation from the observed and expected mortality to determine if any action is necessary.

3.0 Enrollment and DSMB Oversight

In order to ensure that exposure to the device prior to the required submission of the post-market data to FDA will not be continued without evaluation if safety issues arise, enrollment in the Registry will be monitored by the DSMB who will provide recommendations for cessation of enrollment according to stopping rules outlined in the DSMB charter.

4.0 Prognostic Heart Failure Survival Model – SHFM

Mortality rates observed during the Post-Market Registry will be compared to the mortality rate predicted by an established model of survival in heart failure patients. The model employed will be the SHFM model and will be explained in detail in the next section. Data to be collected will include all of the information necessary to estimate survival from this model. The SHFM Score and estimates of survival will be calculated using this data in an Excel Spreadsheet licensed from the University of Washington CoMotion to ensure accuracy of the results.

SHFM. The Seattle Heart Failure Model (SHFM) provides a continuous risk score for each patient that can be expressed as predicted life expectancy and percentage chance of survival to a particular year via a simple one-step exponential transformation. The SHFM was derived with data from the Prospective Randomized Amlodipine Survival Evaluation (PRAISE-1) trial and then validated in a cohort of nearly 10,000 patients across several

outpatient populations: the Losartan Heart Failure Survival Study (ELITE2), Val-HeFT, Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE), an Italian Heart Failure Registry (IN-CHF), and the University of Washington HF clinic. Calculators for the SHFM score have been produced for a variety of platforms and are freely available at http://www.SeattleHeartFailureModel.org. SHFM accurately predicts survival of heart failure patients with the use of commonly obtained clinical characteristics. Importantly, the validation cohorts included patients with a wide range of countries or origins (46), ages (14 to 100 years), EFs (1% to 75%), and heart failure symptoms (NYHA class I to IV), including patients at intermediate and higher risk in whom prediction of risk can be most problematic (Levy et al., 2006). Additionally, 2 of the validation cohorts consisted of patients from a more general population, followed either in a US heart failure clinic (UW) or Italian general cardiology clinics (IN-CHF), representing the populations in whom validation results may be most widely applicable. With the SHFM, a clinician can see the effects on mortality by initiating new HF medications or placing an indicated device. The SHFM has been studied in a wide variety of patient populations ranging from patients on the cardiac transplant list to patients implanted with the Mitra-Clip device. It has been extensively validated, is included in the 2013 AHA/ACC Heart Failure Guidelines and has been cited >900 times. In conclusion, the Seattle Heart Failure Model allows prediction of survival of heart failure patients with the use of easily obtained clinical characteristics. The model provides an accurate estimate of mean, 1-, 2-, and 3-year survival and allows estimation of the effects of adding medications or devices to a patient's regimen.

5.0 Contribution of CMS

CMS has been asked to participate in the development of the post-market registry and it is expected that variables collected may be modified to meet CMS, as well as FDA, requirements. CMS has reviewed the data herein and the plan for the post-market registry. They requested no changes at this time.