

ProRhythm focus AF Clinical Investigation Clinical Trial Synopsis, Enrollment Status and Current Challenges

ProRhythm is engaged in a clinical investigation to evaluate the safety and effectiveness of the High Intensity Focused Ultrasound (HIFU) Ablation System (“focus AF”) in a prospective, randomized, controlled, multicenter clinical trial. The control is medical therapy with anti-arrhythmic drugs (AADs). The primary endpoint will compare the rate of Clinical Success in the treatment group (using the HIFU system) against the control group (medical therapy with AADs). Clinical Success is defined as the achievement of both acute success and chronic success after 12 months of follow-up. The efficacy objective will be met if, at 12 months post-treatment, Clinical Success in the HIFU group is superior to that in the control group.

The major challenge that we face in the execution of this study is the randomization requirement and the effect it has on the enrollment rate. Although we believe that randomization provides the best scientific approach to treatment assignment in a comparative trial, it is not practical for a comparison between two fundamentally different treatment approaches such as an anti-arrhythmic drug and an ablation device. The current ‘standard of care’ for the treatment of paroxysmal AF is interpreted as “best medical therapy with anti-arrhythmic drugs” however; we have found that many patients are routinely managed with other types of medications (e.g., Beta Blockers) and RF ablation. The availability of these treatment options *and* the low efficacy rates associated with anti-arrhythmic drugs makes it difficult to find patients who are willing to risk treatment with a second or third AAD.

During the first 6 months of enrollment for the focusAF study, we asked sites to provide information on each patient screened including the primary reason the patient was deemed ineligible where applicable. Data was collected on a total of 1364 patients of which 1206 failed the pre-screening process (90%). The top reasons for patient ineligibility were:

- Prior Left Atrial Ablation
- Persistent or Chronic AF
- No prior class I or class III anti-arrhythmic drug therapy
- Patient not willing to be randomized to an anti-arrhythmic drug
- Pacemaker/ICD

Of the remaining 158 subjects who were deemed eligible, 93 (59%) refused to be randomized to an anti-arrhythmic drug. In total, only 18 (1%) subjects from this screening group were enrolled into the study.

In an effort to assist the sites with patient recruitment and to gain a better understanding of the recruitment issues, ProRhythm initiated a patient outreach program designed to identify and pre-qualify potential patient referrals through a nurse staffed call center. To date, the call center has pre-screened 1692 patients using an IRB approved script, of which 181 (11%) were pre-qualified and referred onto the sites. Of the 181 pre-qualified referrals, 83 subjects were deemed eligible for enrollment into the study however; 39 (47%) of those subjects have not yet been treated with a class I or class III anti-arrhythmic drug.

In the past 8 months, we have screened over 3000 subjects yet only 41 subjects have been enrolled into the focus AF clinical study. The percentage of screened patients that are eligible *and* willing to participate in our study is approximately 1.4%. We estimate it will take a minimum of 4.9 years to complete enrollment and follow-up of a 240 patient sample size. The number of subjects that will need to be screened to complete enrollment is estimated to be 17,600. Because there are a limited number of qualified investigational sites available to participate in ablation trials and many sites are already involved in multiple studies, we anticipate enrollment rates to slow even further.

FDA believes that randomized, controlled trials are the least burdensome approach for the collection of clinical data to support the safety and effectiveness of ablation devices intended to treat atrial fibrillation. The standard of care is defined as ‘best medical therapy with anti-arrhythmic drugs however; a significant number of patients who qualify for entry into our study do not want to be randomized to a control drug because they have already failed anti-arrhythmic therapy. Those who *are* willing to be randomized are only willing to do so because they have NOT yet tried an anti-arrhythmic drug. Therefore, we are proposing that the panel consider expanding the inclusion criteria to permit enrollment upon failure of drugs routinely used but not indicated for the treatment of AF (eg., beta-blockers). We believe this has the potential to double the number of eligible subjects available for enrollment into our study. In addition, this will also allow investigation of a broader range of ‘indications for use’ which will more closely represent current clinical practice in the treatment of atrial fibrillation.