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EP NEWS AND INNOVATIONS

FDA Approval for Claria MRI™ Quad Cardiac Resynchronization therapy Defibrillator

U.S. Food and Drug Administration (FDA) have approved the Claria MRI™ Quad Cardiac Resynchronization Therapy Defibrillator (CRT-D) SureScan™ device for patients with heart failure. The Claria MRI™ CRT-D is approved for scanning in both 1.5 and 3 Tesla (T) magnetic resonance imaging (MRI) machines, and features EffectivCRT™, a new algorithm that automatically tailors the therapy to individual patients by adjusting pacing rates.

A large percentage of heart failure patients receiving cardiac resynchronization therapy have atrial fibrillation (AF), which can significantly reduce patient response to CRT. The Claria device includes the EffectivCRT Diagnostic, which automatically determines the effectiveness of each left ventricular pace, and the EffectivCRT during AF algorithm, which automatically adjusts pacing rates during AF, without adversely affecting the average heart rate.

Additional features on the Claria device include:

- The AdaptivCRT™ algorithm, which reduces a patient's odds of a 30-day heart failure readmission by 59 percent, and has demonstrated a 46 percent reduction in AF risk compared to echo-optimized biventricular pacing.
- VectorExpress™ 2.0, an automated in-office test that reduces lead programming to two minutes, and reveals clinically actionable information to help physicians select optimal pacing configurations for each patient.
- Attain™ Perfoma™ MRI SureScan™ Quadripolar Leads, which include short bipolar spacing to reduce phrenic nerve stimulation occurrence, steroid on all electrodes, and three shapes for varying patient anatomies.
- SureScan™ MR-conditional labeling for full-body scans without positioning restrictions. Medtronic now offers MR-conditional pacemakers, implantable cardioverter defibrillators (ICDs), insertable cardiac monitors (ICMs) and CRT-Ds. Additionally, patients with certain existing defibrillation leads will be eligible for an MR-conditional ICD or CRT-D, and thus able to access this important imaging technology.

In addition to introducing CRT to the worldwide marketplace nearly 20 years ago, and offering the first MR-conditional CRT-defibrillators in the U.S., the heart failure portfolio includes mechanical circulatory support therapy and impactful heart failure diagnostics and expert analysis through Care Management Services. A Pre-Market Application (PMA) to the FDA for Multiple Point Pacing, which, if approved, would be available with the Claria MRI and Amplia MRI™ CRT-Ds. The Multiple Point Pacing feature is not currently approved for commercial sale in the United States.

Phase 3b Study Shows Significantly Less Bleeding with XARELTO® (rivaroxaban) Compared to Warfarin in People with Non-Valvular Atrial Fibrillation Following Percutaneous Coronary Intervention with Stenting

New Phase 3b results from the PIONEER AF-PCI study met its primary endpoint and showed that both XARELTO® (rivaroxaban) groups had significantly reduced risk of bleeding compared to the warfarin arm in people with non-valvular atrial fibrillation (NVAF) receiving antiplatelet therapy following angioplasty with stenting. The findings of this exploratory, open-label, randomized study were announced during a Late-Breaking Clinical Trial session at the American Heart Association (AHA) Scientific Sessions 2016. A sub-analysis, also showed people in both XARELTO® groups had a significantly reduced risk of being re-hospitalized compared to those in the warfarin arm.

Among people undergoing percutaneous coronary intervention (PCI), also known as angioplasty, a procedure to open clogged heart arteries, five to eight percent have concomitant NVAF. Management of people with NVAF following PCI with stenting is challenging, as the risks of NVAF-related stroke, stent-related blood clots (thrombosis) and bleeding from both oral anticoagulant and antiplatelet therapy must be considered. For people with NVAF following PCI, guidelines recommend "triple therapy", which is a combination of dual antiplatelet therapy (clopidogrel or another thienopyridine plus aspirin) and anticoagulation therapy with a vitamin K antagonist (warfarin), but this regimen comes with recognized increased rates of major bleeding, including intracranial bleeding.

In PIONEER AF-PCI, researchers examined the safety of XARELTO® compared to warfarin in 2,124 people with NVAF who received background antiplatelet therapy following PCI with stenting. The primary endpoint was clinically significant bleeding (composite of TIMI major bleeding, TIMI minor bleeding or bleeding requiring medical attention). Secondary endpoints included the incidence of the components of TIMI clinically significant bleeding, the composite of

major adverse cardiovascular events (cardiovascular death, heart attack or stroke), individual components of the adverse cardiovascular event endpoint and stent-related thrombosis.

Patients were randomized in a 1:1:1 ratio, with one group receiving XARELTO[®] 15 mg once daily plus single antiplatelet therapy (clopidogrel or another thienopyridine) for 12 months, another group receiving XARELTO[®] 2.5 mg twice daily with dual antiplatelet therapy (clopidogrel or another thienopyridine plus aspirin), and a third receiving standard "triple therapy," warfarin with dual antiplatelet therapy. Prior to randomization, the duration of dual antiplatelet therapy (one, six or 12 months) was pre-specified for the two relevant groups and the intended thienopyridine (clopidogrel, prasugrel or ticagrelor). At one year, both XARELTO[®] groups had significantly lower rates of bleeding compared to the group taking warfarin. Specifically, the XARELTO[®] 15 mg group reduced clinically significant bleeding by 41 percent (Hazard Ratio [HR] = 0.59; 95% CI, 0.47 to 0.76; $p < 0.001$; absolute rate 16.8 percent), and the XARELTO[®] 2.5 mg group by 37 percent (HR = 0.63; 95% CI, 0.50 to 0.80; $p < 0.001$; absolute rate 18 percent) compared to the warfarin group (absolute rate 26.7 percent).

This reduction in bleeding for the two XARELTO[®] groups was consistent across multiple subgroups; fatal bleeds were rare and numerically fewer in patients taking XARELTO[®] compared to those taking warfarin.

Although the study was not powered to make conclusions on efficacy, both XARELTO[®] groups showed similar rates of major adverse cardiovascular events compared to the group taking warfarin. Specifically, 6.5 percent of people in the XARELTO[®] 15 mg group and 5.6 percent in the XARELTO[®] 2.5 mg group experienced a major adverse cardiovascular event compared to 6.0 percent in the warfarin group.

A separate sub-analysis of PIONEER AF-PCI showed a reduction in the risk of re-hospitalization or all-cause mortality (due to an adverse event, including bleeding, a cardiovascular cause or other cause) in both XARELTO[®] groups compared to the warfarin group. Specifically, all-cause mortality or re-hospitalization was observed in 34.9 percent of the XARELTO[®] 15 mg group ($p = 0.008$) and 31.9 percent of the XARELTO[®] 2.5 mg group ($p = 0.002$) compared to 41.9 percent of the warfarin group. When looking specifically at re-hospitalization, both XARELTO[®] groups had significantly fewer re-hospitalizations, with 34.1 percent of the XARELTO[®] 15 mg group ($p = 0.005$) and 31.2 percent of the XARELTO[®] 2.5 mg group ($p = 0.001$) being re-hospitalized due to an adverse event compared to 41.5 percent of the warfarin group.

Part of the EXPLORER research program for XARELTO[®], PIONEER AF-PCI is a global, exploratory, randomized, multicenter, Phase 3b clinical study assessing the safety of three treatment strategies in a broad group of people from 26 countries with NVAF who had undergone PCI with stenting.

Unmatched by any oral anticoagulant in the NOAC class in its size, scope and ambition, EXPLORER continues to generate important clinical evidence on the safety and efficacy performance of XARELTO[®] and its potential role in addressing additional critical medical needs. By the time of its completion, more than 275,000 patients will have participated in EXPLORER, which includes ongoing and completed studies, independent registries and non-interventional studies. The EXPLORER program is a collaborative research effort with Bayer and includes six additional indication-seeking programs underway beyond the currently approved six indications in the U.S.

First Data from Multi-Year Study Show Gaps in Non-valvular Atrial Fibrillation Care

Findings from more than 45,000 NVAF patients show less than half were treated with an oral anticoagulant, including those at highest risk of stroke. Data presented at American Heart Association Scientific Sessions will be used to guide future research to help improve patient outcomes.

The final results from the first phase of a three phase, large-scale research collaboration to generate real-world evidence to help inform the development of new medicines, guidelines and interventions. The study assessed oral anticoagulant (OAC) treatment and persistence in NVAF patients, and showed a discrepancy between treatment guidelines and clinical practice at diagnosis and throughout the treatment journey. NVAF is an important risk factor for stroke and clinical trial data has shown that OAC therapy substantially reduces stroke risk in NVAF patients. The findings were presented at the American Heart Association Scientific Sessions 2016 in New Orleans.

The retrospective observational study evaluated records for 45,092 newly diagnosed NVAF patients in the United States from the HealthCore Integrated Research Database from November 1, 2010 to November 30, 2013. Although treatment guidelines recommend OAC treatment for all NVAF patients at high stroke risk (i.e., CHADS2 score ≥ 2), researchers found less than half (41.1 percent) of the study patients were treated with an OAC (warfarin, dabigatran, rivaroxaban or apixaban).

Compared to untreated patients (n = 26,543), treated patients (n = 18,549) were younger (mean of 70 ± 12.2 years vs. 71 ± 14.3 years), more likely to be male (59.7% vs. 52.5%), with higher CHADS2 scores (stroke risk; 2.03 ± 1.3 vs. 1.98 ± 1.4) and lower HEMORR2HAGES scores (bleed risk; 2.55 ± 1.8 vs. 2.8 ± 1.9).

Patients at the highest risk of stroke, however, did not have the highest treatment rate. Higher stroke risk (measured by CHADS2 score) was associated with a higher bleed risk (measured by HEMORR2HAGES score) in all patients suggesting the risk of bleeding may be a critical component in OAC treatment decision making.

Among those patients who were treated with an OAC (n = 18,549), the majority initiated treatment on warfarin (60.1%). Nearly one-fourth (23%) of treated patients stopped taking their medication within three months and more than half (55%) stopped within the first year. At follow-up (average of 2.25 years later), 72.7 percent of patients had stopped taking their medication.

As follow up to this research, there will be surveying of patients and their providers to gain a better understanding of disease management and adherence challenges, treatment decision-making factors and treatment experiences. The next phases of the project are currently underway and results are anticipated in 2017.

This is a five-year research project to identify and address unmet medical needs across populations of mutual interest. The collaboration will enable the generation of real-world evidence and develop health economic and outcomes data to inform the development and evaluation of new medicines, guidelines and interventions.

The first research topic under the agreement is non-valvular atrial fibrillation (NVAf). With the entry of newer anticoagulant therapies, after more than five decades of warfarin use, there is an important opportunity to understand how NVAf is being managed in a new era of treatment.

This can explore issues related to appropriate use of existing and new therapies and interventions and the impact these have on clinical and economic outcomes that matter the most to patients.

CE Mark for a New Steerable Sheath with a Novel Approach for Transseptal Puncture and Left Atrial Navigation

A new steerable sheath with a novel approach of transseptal puncture and left atrial navigation to treat multiple clinical indications, announced today that it has received its first CE-Mark for its TSP Crosser™ Transseptal Access System.

A new approach to the growing need for safe access to the left atrium. With the increased availability of transcatheter left atrium procedures, there is a growing need to provide surgeons with tools that allow accurate, quick and safe access to the left atrium. TSP Crosser is an advanced transseptal puncture system with a built-in steering mechanism, effective in a wide range of procedures:

- LAA Appendage Closure
- Mitral Valve Repair
- Mitral Valve Replacement
- EP Ablation Treatments

The TSP Crosser™ Transseptal Access System combines a sheath, dilator and a flexible puncturing needle in a single integrated system for controlled LA access and enhanced safety during transseptal catheterization procedures. A radiopaque loop wire is positioned at the distal end of the steerable sheath to aid in localizing the fossa ovalis. The flexible puncturing needle allows deflection and orientation using the steerable sheath, positioning it in the optimal spot to puncture the fossa ovalis for transseptal access. A handle equipped with a rotating collar deflects the steerable sheath tip 180° to each side after crossing into the fossa ovalis. Earlier this year, it successfully completed a 10-patient multi-center clinical study in Europe to study the safety and performance of the TSP™ Transseptal Access System.

New tech to treat atrial fibrillation, the most common arrhythmia

Researchers have partnered to develop a more efficient system for detecting and treating atrial fibrillation that will be in hospitals soon.

Atrial fibrillation is the most common serious abnormal heart rhythm or 'arrhythmia' and is characterized by rapid and irregular beating. It causes the patient to be unable to live a normal life, and significantly reduces life expectancy. This type of arrhythmia is complicated, usually requiring surgical intervention in the form of catheters inserted into the

heart to record the electrical activity in the atria and identify the problem region and potential target for subsequent surgical treatment.

However, even using this method it is difficult to identify the exact source of the arrhythmia and in around 40% of cases the surgery is ineffective and must be repeated.

Researchers have developed a new system that geolocates cardiac arrhythmias in real time, guiding physicians during cardiac ablation, and reducing the cost and duration and increasing the effectiveness of surgical intervention. This new technology is able to generate a map of a patient's cardiac activity in both atria in real time from the combination of surface and non-invasive intracardiac recordings.

Currently, both the detection and treatment of arrhythmias are carried out using invasive cardiac catheterization processes. These processes, although they allow cardiac activity to be recorded and, where the arrhythmia follows a consistent pattern, a target for ablation to be localized, they are limited.

Meanwhile, another technique known as non-invasive reconstruction of cardiac activity is receiving much attention as a means of improving the effectiveness of the detection and treatment of atrial fibrillation. However, the high cost and complexity of this method means it is not being incorporated into clinical practice.

The main differentiating features of the device, patented and developed, is the way in which the 3-D image of the patient's body is obtained and the simultaneous use of invasive and non-invasive information to reliably reconstruct electrical activity in the atria.

Faster, non-invasive method to determine the severity of a heart failure

Heart failure is a very common problem when the heart is no longer able to pump enough blood through the body. Methods currently employed to determine the severity of a heart failure are very limited. Researchers have therefore developed a method that is very quick, non-invasive, cost-effective and can be performed at the hospital bedside. Moreover, this method appears to have a predictive value for whether or not a double pacemaker will be successful.

To get the right treatment, it is important to measure how well the heart is still able to do its job. There are currently various methods for doing this, but all have their limitations. Sensors often need to be placed in the large arteries, via the shoulder or neck, and that is quite an invasive procedure. MRI is a possibility, but not for patients that are seriously ill. Patients that are short of breath nearly always undergo blood analysis, a method that examines the concentration of a particular protein in the blood and provides an excellent indicator, but it takes several hours before the outcome is known.

Researchers have developed a patient-friendly method that uses an echo scanner, which is known mainly for echoes performed during pregnancy, to determine the severity of heart failure. To do this, they measure the time it takes for the blood to travel from the heart's right ventricle through the lungs to the left ventricle, which is responsible for pumping oxygenated blood through the body. In order to measure this pulmonary transit time (PTT), they inject harmless microbubbles that can be seen clearly by the echo scanner. Researchers then look at the heart and see how long it takes for the bubbles to get from the right to the left ventricle.

It may seem simple enough but there was a significant scientific challenge in calculating an unequivocal PTT for the observed microbubbles that get dispersed in the blood flow. But once that had been solved, researchers compared the transit time with a number of existing indicators, developing a similar method on the basis of MRI. Comparisons revealed that the PTT measured with the echo scanner provides an excellent indicator for the severity of a heart failure. A healthy heart pumps the blood quickly through the lungs. The longer the PTT, the less well the heart performs. The researchers examined subjects whose heart muscle no longer contracted well, which is the most common type of heart failure. Before the method can be used, there is still work to be done. For example, if it is to be both practical and fast, the analysis will have to be automated.

Another aspect being studied is the extent to which the PTT is able to predict the success of a double pacemaker, whose primary objective is to restore the synchronicity of the two ventricles of the heart. Researchers indeed found that there was a fairly firm relationship between the transit time and the success rate. The breaking point is 12.5 seconds; above that, the chance of the pacemaker enabling the heart to perform better reduces. But any application of this indicator requires more research. Because the method does not appear to be completely accurate in the prediction, researchers expect it to be useful in combination with other indicators.

New sensor to monitor heart failure symptoms, reduce hospitalization

Cardiologists have introduced a new implantable miniaturized, wireless monitoring sensor to manage heart failure and reduce the number of times people with this life-threatening disease need to be hospitalized.

The CardioMEMS HF System measures pulmonary artery pressure, which is an indirect measure of worsening heart failure. A monitor built into a pillow allows the system to transmit daily information from patients' homes directly to the heart failure team, allowing for personalized and proactive care to reduce the likelihood of hospitalization.

There are more than 5 million people living with heart failure in the United States. Fluid retention is a serious problem for people with heart failure and is often not obvious until it impedes breathing. When the heart muscle isn't strong enough to pump all the blood from the left ventricle, pressure inside the heart rises and causes shortness of breath. The CardioMEMS device records those changes and sends the information to heart failure experts, allowing them to consider changes in therapy.

Getting a pacemaker soon after heart valve replacement linked with worse outcomes

Patients who undergo minimally invasive heart valve replacement, known as TAVR, sometimes develop heart rhythm problems that necessitate placement of a permanent pacemaker. However, when a pacemaker is needed soon after TAVR, patients often have worse outcomes than those who did not need a pacemaker, according to a new study. The study shows that the risks are both short- and long-term and include lengthier hospital and intensive care unit stays as well as a greater risk of death.

Transcatheter aortic valve replacement, or TAVR, is a relatively new, minimally invasive surgical procedure that repairs the aortic heart valve without needing to remove the old valve. Often a patient spends less time recovering and avoids some of the risks associated with open-heart valve replacement. It is typically recommended for patients who are not able to undergo a traditional open-heart procedure--many times, these are people in their 80s or 90s who have other medical conditions that make an open-heart surgery a less preferred option.

Using data from the STS/ACC TVT Registry, researchers analyzed patients undergoing TAVR in the United States at 229 sites between November 2011 and September 2014 to see how permanent pacemaker implantation after having TAVR affected them.

Of the 9,785 study participants, 651 needed a permanent pacemaker within 30 days of the TAVR procedure. Those who needed a permanent pacemaker had a slightly longer hospital stay as well as longer reported hours in the intensive care unit. They also had an increased risk of death from any cause at one year. In addition, they found that the combination of death from any cause or heart failure hospitalizations was increased at one year.

If confirmed, these results urge engineers, device manufacturers and physicians to work even harder to find ways to reduce the rate of permanent pacemaker placement after TAVR.

Impella Quality (IQ) Assurance Program and Insight from Largest Database of Real-World Evidence of High-Risk PCI and Cardiogenic Shock Patients

The mission of the program is to improve real-world outcomes in Protected PCI and cardiogenic shock patients through training, education and utilization of clinical guidelines, protocols and best practices derived from observational quality assurance data (IQ), IRB approved registry data (cVAD) and IDE approved FDA studies.

These data resources include IQ Database, which is a collection of observational quality assurance data on over 95% of Impella patients since the Impella 2.5™ heart pump's introduction to the United States in 2008. This holds more than 44,000 Impella case entries. This IQ database, combined with additional clinical data collected in the cVAD Registry™ and FDA pre- and post-market studies, has helped identify best practices and protocols that are linked to the highest survival and native heart recovery rates at the Impella hospitals. For example, the placement of Impella prior to doing a PCI in cardiogenic shock appears to improve outcomes.

This is being shared with hospitals around the country as part of comprehensive education and training initiatives with the goal of positively affecting both survival and recovery outcomes for this very high-risk patient population.

The goal of the IQ Program is to also complement these best practices with a clinical field team, consisting of over 250 individuals in the United States. This experienced team, which includes physicians and nurses, has expertise in hemodynamic support and provides 24x7 onsite clinical assistance from the cath lab to the Intensive Care Unit (ICU). It also provides 24x7 call center support staffed by experienced cardiac nurses and technologists. From an educational perspective,

this has created case-based learning tools and reinforces guideline-based appropriate use treatment. The program also encourages the use of After Action Reviews, which is a continuous learning tool that hospital Heart Teams can implement to improve practices after each case. In addition, the appropriate use rationale includes seven society guidelines for the use of pVADs, supported by a compendium of resources on improved outcomes and cost effectiveness.

The Impella products offer the unique ability to stabilize the patient's hemodynamics and unload the heart, which allows the muscle to rest and potentially recover its native function. Impella 2.5 received FDA PMA approval for high risk PCI in March 2015. Impella 2.5, Impella CP, and Impella 5.0 received FDA PMA approval for cardiogenic shock in the setting of acute myocardial infarction/heart attack or after heart surgery. These are the first and only percutaneous temporary ventricular support devices that are FDA-approved as safe and effective for the cardiogenic shock indication. The Impella product portfolio, which is comprised of Impella 2.5, Impella CP, Impella 5.0, Impella LD, and Impella RP, has supported over 40,000 patients in the United States.

New Study Suggests Extended Continuous Cardiac Monitoring is More Useful than Holter Monitoring for Adult Congenital Heart Disease Patients

Arrhythmias are a leading cause of death in adults with congenital heart disease. Study results presented during the American Heart Association (AHA) Scientific Sessions suggest that extended continuous cardiac monitoring using the Zio[®] system is more useful for arrhythmia detection than Holter monitoring in patients with adult congenital heart disease (ACHD).

The study, "The Days of the Holter Monitor Are Numbered: Extended Rhythm Monitoring Detects More Clinically Significant Arrhythmias in Adults with Congenital Heart Disease," analyzed 387 ACHD patients' results from extended continuous cardiac monitoring with the Zio system from June 2013 to May 2016. Fifty-one percent of these patients were found to have a significant arrhythmia, fewer than half of which were noted during the first 48 hours of monitoring.

Traditional Holter monitors are often used to assess arrhythmia burden in ACHD patients. However, only 24 to 48 hours of data can be collected at a time. Extended continuous monitoring utilizing the Zio system can record up to two weeks of continuous cardiac rhythm data, allowing it to detect significant arrhythmias beyond the Holter Monitor's 48-hour monitoring period.

Zio is the first long-term continuous monitoring system that is supported by extensive clinical data with peer-reviewed publications, and enables diagnosis earlier in the clinical pathway to improve patient outcomes.

Treating cardiac arrhythmia more gently: development of a biohybrid cardiac pacemaker

In a joint research project, developments for a biohybrid cardiac pacemaker is being researched. The goal of this new approach is to treat cardiac arrhythmia more gently by a targeted optical stimulation of the cardiac muscle and other muscle groups.

The research on biohybrid implants for the light-induced cardiac excitation, defibrillation and stimulation of skeletal muscles is the goal of this project. To implement this innovative therapeutic concept, the partners are bringing together the latest findings from the fields of photonics, optogenetics, nanotechnology and medicine.

The new technology is based upon an innovative approach to stimulate a contraction of the cardiac muscle: While conventional cardiac pacemakers work with electrical impulses, the new method shall use optical impulses. Thus, it is not an electrical stimulation but light that causes the cardiac muscle to contract.

Another novelty is the material: A part of the pacemaker shall consist of biological material. With the pacemaker being made of the patients' own cells, rejection reactions of the human body can be minimized. Integrated in a hydro gel, these cells are doped with upconverting nanoparticles (UCNP). These are required to cause a contraction in reaction to the optical stimulation. The impulse is imparted to the surrounding cells, and thus the cardiac muscle contracts.

With this altered approach not only an improved treatment of cardiac arrhythmia will be possible. At a later stage, a biohybrid defibrillator shall be developed, too. In that way, long-term consequences of the treatment – for example the scarring of the tissue – can be reduced or even completely avoided.

The project has an unusually short development time, because it can make use of already existing results for sub-projects. The challenge, however, is to combine these results and to prepare them for use in the pacemaker. The researchers focus on the coupling and distribution of light in the cardiac muscle.

Study Validating Safe and Efficient In-Office Insertion of BioMonitor 2 Cardiac Monitor

Atrial fibrillation is a leading cause of stroke and heart failure. It has been announced that the first patients have been enrolled in the BioInsight clinical study. The study evaluates the safety and feasibility of performing the minimally invasive BioMonitor 2 insertion procedure in an office setting.

BioMonitor 2 is an insertable cardiac remote monitor with ProMRI® technology that is placed underneath a patient's skin to help physicians accurately detect and diagnose atrial fibrillation and syncope (fainting). BioMonitor 2 provides the highest signal amplitude on the market, which leads to excellent sensitivity for improved reporting accuracy. The device can also be used to monitor atrial fibrillation in patients who have undergone ablation procedures. More than 2,000 BioMonitor 2 devices have been sold in the US since FDA approval in April 2016.

The BioInsight study is a multi-center, prospective, non-randomized post-market study. Participants will receive BIOTRONIK's BioMonitor 2 via in-office insertion and will be evaluated for 90 days to monitor for any potential adverse events, including infection and bleeding.

European Full Market Release of EnSite Precision™ Cardiac Mapping System

When physicians use catheter ablation to treat abnormal heart rhythms (arrhythmias), several catheters are inserted into the heart. Diagnostic catheters record electrical information from the heart and display it in a three-dimensional anatomical model, which is used to study the abnormal rhythm.

Another catheter is used for the actual ablation. The physician positions the ablation catheter so it lies on or very close to the targeted tissue. The small area of heart tissue under the tip of the ablation catheter is heated by high-frequency energy, creating a lesion or tiny scar. As a result, this tissue is no longer capable of conducting or sustaining the arrhythmia.

There is a full market release of EnSite Precision™ cardiac mapping system and new Sensor Enabled™ tools in Europe. The new platform is now installed and active in more than 100 sites across Europe and has been used to support more than 5,000 ablation cases since the system's CE Mark approval in January 2016.

Used in ablation procedures to visualize and navigate catheters in the heart, the EnSite Precision™ cardiac mapping system provides highly detailed anatomical models and maps to effectively enable diagnosis of a wide range of arrhythmias (abnormal heart rhythms) — including complex cases of atrial fibrillation and ventricular tachycardia — and guide therapy. The system combines magnetic and impedance technologies to transform procedures with intuitive automation, expanded procedural options and tailored care using superior flexibility and it allows effective management of patients through greater accuracy.

The EnSite Precision™ cardiac mapping system is flexible and enhances workflow efficiency by allowing physicians to optimize mapping of the heart chambers using the new Sensor Enabled toolset and customize procedures to address the circumstances of each case. The FlexAbility™ Ablation Catheter, Sensor Enabled™ can enhance procedural versatility and precision; it combines an advanced handle with a bendable irrigated catheter tip to conform to the cardiac anatomy allowing for effective lesion formation. Designed for advanced handling and maneuverability, the Advisor™ FL Circular Mapping Catheter, Sensor Enabled™ allows for precise navigation and model creation with impedance-field flexibility and magnetic-field stability.

The EnSite Precision cardiac mapping system also allows real-time catheter navigation to occur using minimal fluoroscopy, thus reducing potential for risks associated with excessive radiation exposure for patients and clinicians.

In addition to Europe, the EnSite Precision cardiac mapping system is available in other markets, including Hong Kong and Singapore.

Initiation of Patient Enrollment in Additional Phase 2 Study Of AIR001 For The Treatment Of Heart Failure With Preserved Ejection Fraction

Heart failure is a leading cause of morbidity and mortality among the elderly worldwide and is the primary diagnosis in more than 1 million hospitalizations each year, with medical costs projected to rise to more than \$50 billion in the U.S. alone by 2030.

There is a report that the first patient has been enrolled in an investigator-sponsored Phase 2 study of AIR001, for the treatment of heart failure with preserved ejection fraction (HFpEF). The Inorganic Nitrite to Amplify the Benefits and Tolerability of Exercise Training (INABLE-TRAINING) in HFpEF study will evaluate AIR001's potential to improve the

clinical responses to exercise training in individuals with HFpEF. The INABLE-TRAINING study is expected to enroll approximately 68 patients who will undergo 12 weeks of cardiac rehabilitation, including exercise training, and will be randomized to receive either AIR001 or placebo inhalation solution through the training period. The primary endpoint of the study will be the change in exercise capacity as measured by peak oxygen consumption.

This is a Phase 2 randomized, double-blind, parallel-group placebo-controlled clinical trial testing whether inhaled AIR001 (sodium nitrite solution), as compared to inhaled placebo, can enhance the benefits from chronic exercise training (ET) in subjects with HFpEF. All subjects will undergo 12 weeks of ET. Participants will be randomized to receive inhaled AIR001 three times daily or inhaled sodium chloride (placebo) three times daily during the study period. Study subjects will wear accelerometry devices to track daily activity levels at home. After 12 weeks of ET as part of standard cardiac rehab, subjects will repeat the assessment of cardiovascular function and exercise capacity as performed at study entry to assess efficacy at a final visit.

The Phase 2 study has 2 aims. First, determine whether treatment with inhaled AIR001 in addition to ET for 12 weeks improves exercise capacity and hemodynamic reserve in HFpEF. Expired gas analysis, inert gas (C₂H₂) rebreath, and echocardiography will be performed during rest and exercise to measure oxygen consumption (VO₂), CO, and hemodynamics before and after completion of 12 weeks of ET with inhaled NO₂- vs ET with inhaled placebo. Second, determine whether treatment with inhaled AIR001 in addition to ET for 12 weeks increases daily activity levels and quality of life (QOL), and reduces symptoms of effort intolerance during ET. Subjects will use externally worn accelerometer devices to track daily physical activity. Tolerability of ET will be assessed by Borg perceived effort and dyspnea scores. Large and small vessel endothelial function (brachial and digital arteries) and QOL will also be assessed. Secondary endpoints include cardiac output reserve, peak exercise workload, rest and exercise hemodynamics assessed by echocardiography, Borg dyspnea and fatigue scores recorded during ET, endothelial function assessed by tonometry and brachial artery flow mediated dilation, QOL assessed by the Kansas City Cardiomyopathy Questionnaire. (ClinicalTrials.gov Identifier: NCT02713126)

AIR001 is a sodium nitrite solution for intermittent inhalation via nebulization. Nitrite is a direct vasodilator and can be recycled *in vivo* to form nitric oxide (NO) independent of the classical NO synthase (NOS) pathway. Nitrite mediated NO formation has several beneficial effects, including dilation of blood vessels and reduction of inflammation and undesirable cell growth. Generation of NO from sodium nitrite is not dependent upon endothelial function and is enhanced in the setting of tissue hypoxia and acidosis, conditions in which NOS activity typically is depressed. In early clinical studies, AIR001 demonstrated positive hemodynamic effects with reductions observed in right atrial pressure and pulmonary capillary wedge pressure, as well as improvements in mean pulmonary artery pressures, cardiac output, and exercise tolerance as measured by six-minute walk distance. In a randomized, double-blind, placebo-controlled Phase 2a study of AIR001 in patients with heart failure with preserved ejection fraction (HFpEF) (n = 26), the AIR001 treatment group showed a statistically significant decrease in pulmonary capillary wedge pressure during exercise compared to the control group and AIR001 was generally well-tolerated.

Results From COSMIC-HF Trial Showing Omecamtiv Mecarbil Significantly Improved Cardiac Function In Patients With Chronic Heart Failure

Heart failure is a condition that affects more than 23 million people worldwide, about half of whom have reduced left ventricular function. It is the leading cause of hospitalization and readmission in people age 65 and older. Despite broad use of standard treatments and advances in care, the prognosis for patients with heart failure is poor. An estimated one in five people over the age of 40 are at risk of developing heart failure, and approximately 50 percent of people diagnosed with heart failure will die within five years of initial hospitalization.

The results from a Phase 2 clinical trial evaluating omecamtiv mecarbil in patients with chronic heart failure have been published. The COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial met its primary pharmacokinetic objective and showed statistically significant improvements in all pre-specified secondary measures of cardiac function in the treatment group receiving pharmacokinetic-based dose titration. The results were initially presented as a Late-Breaking Clinical Trial at the American Heart Association (AHA) Scientific Sessions.

The trial, which evaluated 448 patients with chronic heart failure and left ventricular systolic dysfunction, showed that dose titration controlled patient exposure to omecamtiv mecarbil. Patients were randomized 1:1:1 to receive either placebo or treatment with omecamtiv mecarbil dosed as 25 mg twice daily or 25 mg with dose escalation to 50 mg twice daily, depending on plasma concentrations of omecamtiv mecarbil after two weeks of treatment.

The pharmacokinetic-based dose titration strategy was designed to maintain patient exposure to omecamtiv mecarbil in the targeted plasma concentration range. Approximately 53 percent of patients in the dose titration group were escalated to a dose of 50 mg twice daily.

Following 20 weeks of treatment, statistically significant improvements were observed in all pre-specified secondary endpoint measures of cardiac function in the dose titration group, compared to placebo. Systolic ejection time increased by 25.0 msec ($p < 0.0001$), stroke volume increased by 3.6 mL ($p = 0.0217$) and heart rate decreased by 3.0 beats per min ($p = 0.0070$). Left ventricular end-systolic and end-diastolic dimensions decreased by 1.8 mm ($p = 0.0027$) and 1.3 mm ($p = 0.0128$), respectively, and were associated with statistically significant reductions in left ventricular end-systolic and end-diastolic volumes. N-terminal pro-brain natriuretic peptide (NT-proBNP) decreased by 970 pg/mL ($p = 0.0069$). In pre-specified exploratory analyses of the dose titration group, placebo-corrected reductions in NT-proBNP persisted four weeks after stopping omecamtiv mecarbil, decreasing further to 1,306 pg/mL ($p = 0.0006$). The data also showed increases in fractional shortening at week 20 compared to placebo in the dose titration group.

Adverse events (AEs), including serious AEs, in patients on omecamtiv mecarbil were comparable to placebo. The incidence of adjudicated deaths (3 percent died on placebo, 1 percent died on omecamtiv mecarbil 25 mg twice daily, 2 percent died on omecamtiv mecarbil dose titration), myocardial infarction (1 percent on placebo, 0 percent on omecamtiv mecarbil 25 mg twice daily, 1 percent on omecamtiv mecarbil dose titration) and unstable angina (0 percent on placebo, 1 percent on omecamtiv mecarbil 25 mg twice daily, 0 percent on omecamtiv mecarbil dose titration) was similar. Other cardiac AEs were generally balanced between placebo and active treatment groups. In patients receiving omecamtiv mecarbil compared to placebo, cardiac troponin increased by 0.001 ng/mL and 0.006 ng/mL (median change from baseline at week 20) in the 25 mg twice daily group and dose titration group, respectively. Events of increased troponin ($n = 278$ across all treatment groups) were independently adjudicated and none were adjudicated as an episode of myocardial ischemia or infarction.

COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) was a double-blind, randomized, placebo-controlled, multicenter, Phase 2 trial designed to evaluate an oral formulation of omecamtiv mecarbil in chronic heart failure patients with reduced ejection fraction. The trial consisted of two parts, a dose escalation phase and a larger and longer expansion phase. The dose escalation phase, which completed in 2013, assessed the pharmacokinetics and tolerability of three oral modified-release formulations of omecamtiv mecarbil and was used to select one formulation for further evaluation in the expansion phase. In the dose escalation phase, 96 patients were randomized 1:1:1 to placebo or one of three oral modified-release formulations of omecamtiv mecarbil in two cohorts (25 mg twice daily or 50 mg twice daily). Each patient cohort was followed for 35 days.

The expansion phase evaluated 448 chronic heart failure patients with reduced ejection fraction who were dosed with the selected oral formulation of omecamtiv mecarbil for 20 weeks and followed for a total of 24 weeks. Patients were randomized 1:1:1 to receive either placebo or treatment with omecamtiv mecarbil 25 mg twice daily or 25 mg with dose escalation to 50 mg twice daily, depending on plasma concentrations of omecamtiv mecarbil after two weeks of treatment. The pharmacokinetic-based dose titration strategy was designed to maintain patient exposure to omecamtiv mecarbil in a targeted plasma concentration range; approximately 53 percent of patients in the dose titration group were escalated to a dose of 50 mg twice daily.

The primary endpoints for the expansion phase were to assess the maximum and pre-dose plasma concentration of omecamtiv mecarbil. The secondary endpoints were to assess changes from baseline in systolic ejection time, stroke volume, left ventricular end-systolic diameter, left ventricular end-diastolic diameter, heart rate and NT-proBNP (a biomarker associated with the severity of heart failure) at week 20, as well as the safety and tolerability of omecamtiv mecarbil including incidence of adverse events from baseline to week 24.

COSMIC-HF was not designed to assess the impact of omecamtiv mecarbil on cardiovascular outcomes in heart failure patients.