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RESULTS FROM LARGEST STUDY OF ANTI-REJECTION THERAPY FOR HEART TRANSPLANT PATIENTS WILL BE RELEASED AT ISHLT MEETING

San Diego, Calif. April 14, 2011 – New results from the largest multicenter clinical trial for heart transplant patients will be released this week at the International Society for Heart and Lung Transplantation (ISHLT) 31st Annual Meeting and Scientific Sessions in San Diego. Results show clinical benefit for the use of Everolimus in heart transplant patients.

The trial includes 721 randomized patients at 67 medical centers spanning 5 continents. The research compared the efficacy of anti-rejection therapy Everolimus with the current standard of care Mycophenolate Mofetil (MMF).

Research to be presented at the ISHLT Meeting includes:

- **Everolimus-Based Immunosuppression Versus Conventional Treatment in Long-Term Heart Transplanted Patients: Three Years Results of a Prospective Randomized Trial** (abstract 2) is a featured abstract during the Thursday morning Opening Plenary Session at 9:30am PDT.
- **Reduction of Cardiac Allograft Vasculopathy with Everolimus over Mycophenolate Mofetil: Intravascular Ultrasound Results of a Randomized Multicenter Trial** (abstract 52) will be presented Thursday during an afternoon symposium at 2:00pm PDT.
- **Everolimus with Reduced CsA vs MMF with Standard CsA Exposure in *De Novo* Heart Transplant Recipients: 12 Month Efficacy and Safety Analysis** (abstract 55) will be discussed during the same Thursday symposium at 2:45pm PDT.
- **Heart Transplant Recipients Treated with Everolimus Have Less Increase in Intimal Thickness vs MMF, Irrespective of Lipid Values** (abstract 57), will also be presented on Thursday afternoon, 3:15pm PDT.

HIGHLIGHTS

Intravascular Ultrasound Results

One study, specifically looking at intravascular ultrasound (IVUS) results, showed a robust benefit with Everolimus relative to Mycophenolate Mofetil (MMF) by IVUS at the end of one year. This study included 189 patients: 88 patients

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randomized to Everolimus at low dose of 1.5 mg/day and 101 randomized to MMF. There was no significant difference between the groups with regard to baseline demographics.

“The fact that data was so robust in all IVUS parameters is very significant and clinically applicable” according to the principal investigator Jon Kobashigawa, MD, Cedars-Sinai Heart Institute, Los Angeles.

The data show that a significantly smaller percentage of patients had a change in intimal thickness greater than 0.5mm during the first year after heart transplant in the Everolimus group versus the MMF group. In addition to a benefit in intimal thickness there was also a significant improvement in three dimensional intimal volume in the Everolimus group. According to Dr. Kobashigawa, this data is crucial, because previous IVUS studies have shown high morbidity and mortality rates at 5 years in those patients with an increase in intimal thickness greater than .5 mm in the first year after heart transplantation.

On average, all subgroups in the study showed clinical benefit with Everolimus, including patients over 50 years of age, both males and females, diabetics, and patients with previous disease.

Everolimus with Reduced CsA

These investigators compared Everolimus given with reduced levels of Cyclosporine (CsA) with MMF using standard levels of CsA, specifically looking at the drugs’ efficacy and affect on kidney function.

Researchers found that Everolimus does not appear to be superior to MMF in terms of acute cellular rejection, but that adverse effects on the kidneys can be prevented by using lower doses of CsA.

According to principal investigator, Howard J. Eisen, MD, Drexel University College of Medicine, Philadelphia, using a lower dose of CsA also showed a significant reduction in transplant coronary disease as described above and less infection with cytomegalovirus (CMV).

In this study, 282 patients received Everolimus at 1.5mg/day dose, 168 received Everolimus at 3mg/day dose and 271 received MMF. Investigators noted that the 3mg arm was terminated early by the Data Safety Monitoring Board due to higher mortality.

“All immunosuppression drugs are complicated and require experience with these drugs to determine the best way to use them. This trial has provided

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enough experience with Everolimus to teach us how to use this medication to help patients. If Everolimus is combined with a low dose of CsA and we can minimize the use of immunosuppression therapy post transplant, then Everolimus reduces the likelihood of severe complications, like transplant coronary disease and CMV," said Dr. Eisen.

Researchers noted that further study is required to answer additional questions, such as those related to the issue of malignancy. Other studies suggest a potential beneficial effect with the class of drugs that includes Everolimus in blocking a certain protein leading to malignant growth, but further research is needed to demonstrate real benefit.

Dr. Eisen concluded that this research is very promising. MMF is a very effective drug, and results showing the same rate of rejection with Everolimus are not surprising. However, the positive results demonstrating that using less CsA to reduce the likelihood of renal failure with the same incidence of rejection and a reduced incidence of transplant coronary disease and CMV confirm that Everolimus is an effective anti-rejection therapy for heart transplant patients.

About ISHLT

The International Society for Heart and Lung Transplantation (ISHLT) is a not-for-profit organization dedicated to the advancement of the science and treatment of end-stage heart and lung diseases. Created in 1981, the Society now includes more than 2,200 members from 45-plus countries, representing a variety of disciplines involved in the management and treatment of end-stage heart and lung disease.

ISHLT maintains two vital databases. The International Heart and Lung Transplant Registry is a one-of-a-kind registry that has been collecting data since 1983 from 223 hospitals from 18 countries. The ISHLT Mechanical Circulatory Support Device (MCSD) database has been collecting data since 2002 with the aim of identifying patient populations who may benefit from MCSD implantation; generating predictive models for outcomes; and assessing the mechanical and biological reliability of current and future devices. In Fall 2006, ISHLT released the first international guidelines for heart failure patient management. For more information, visit www.ishlt.org.

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