

News Release

For Immediate Release

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THREE CLINICAL STUDIES DEMONSTRATE ONCE-DAILY MODIFIED RELEASE PROGRAF® FORMULA TO BE PROMISING TREATMENT OPTION

*Additional Milligram to Milligram Conversion Study Shows
Equivalency of Prograf to MR Prograf*

SEATTLE, May 24, 2005 – Two studies presented today at the 6th American Transplant Congress (ATC) demonstrate the safety and efficacy of once-daily Modified Release (MR) Prograf® (TAC or tacrolimus) as compared to standard Prograf. MR Prograf is an extended release version of the FDA-approved twice-daily formulation of Prograf, a leading immunosuppressive agent for patients with kidney or liver transplants.

Typically, transplant recipients are prescribed a multitude of medications that require dosing at various times throughout the day. According to a study conducted by the American Heart Association*, one of the major factors contributing to patient non-compliance is the complexity of their medication regimen.

"Once daily dosing provides a benefit to the patient because of its convenience," said Rita Alloway, PharmD, BCPS, research professor at the University of Cincinnati and lead investigator of the liver study. "Medication compliance studies** have shown compliance tends to fall as dosing frequency increases above once daily. Therefore the availability of a once-daily formulation, such as MR Prograf, could increase the number of patients adhering to their medication regimen, increasing the ability to maintain a healthy graft."

The two studies, conducted in stable liver recipients and stable kidney recipients, provide one year follow-up data of a milligram-to-milligram comparison of the dosing regimens of Prograf, demonstrating the equivalency of the two versions of the drug. Results from the study of stable kidney patients also showed a decrease in the need for agents used to treat hypertension and

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hyperlipidemia vs. twice-daily Prograf, while there was no change in the need for medications to treat diabetes. A third study, designed to evaluate Prograf exposure and trough levels in stable pediatric liver recipients converted to the modified release formula, found that the steady-state pharmacokinetics of tacrolimus on MR Prograf is equivalent to Prograf after a milligram-to-milligram conversion.

Stable Kidney Recipients Converted from Prograf® BID to MR Prograf®

The study was designed to assess safety and efficacy after one year of stable kidney patients converted from the administration of Prograf BID (administered twice daily) to once-daily Modified Release (MR) Prograf. Sixty-seven patients who entered the long-term extension on MR Prograf after completing the pharmacokinetic portion of the study (0-35 days) were evaluated for MR Prograf dosing and trough levels, laboratory values, concomitant medications, graft survival and adverse events. The mean dose of MR Prograf at conversion was 5.7 mg/day (1-19 mg/day) and 5.9 mg/day (1-17 mg/day) at one year. At conversion, the mean tacrolimus trough concentration was 6.8 ng/mL (3.0-11.9 ng/mL), at one year it was 6.5 ng/mL (1.7 -12.8 ng/mL). The mean baseline serum creatinine value was 1.37 mg/dL (range 0.7-3.6 mg/dL) and 1.51 mg/dL (range 0.7-3.1 mg/dL) at one year. No significant changes in any laboratory parameter were observed during the follow-up. From conversion to one year, the use of anti-hypertensive and lipid lowering agents decreased by 8 percent and 7percent, respectively. In all, the 63 renal transplant patients who completed the study remained stable in the first year following conversion from Prograf BID to MR Prograf. Study authors concluded that the one-year follow-up confirms the safety and efficacy of mg:mg conversion from Prograf BID to MR Prograf.

145 A ONE YEAR FOLLOW-UP STUDY OF STABLE KIDNEY TRANSPLANT RECIPIENTS CONVERTED FROM TWICE DAILY PROGRAF TO ONCE DAILY MODIFIED RELEASE TACROLIMUS. Steven Steinberg. May 22, 2005, 12:30 pm, Poster session: Kidney Immunosuppression: New Agents (12:30 PM-2:00 PM), Hall 4F.

Stable Liver Recipients Converted from Prograf® BID to MR Prograf®

A similar study was conducted at the one year follow-up point to assess the conversion of stable liver patients converted to Modified Release (MR) Prograf once-daily from a twice-daily Prograf regimen. Seventy patients were enrolled in the pharmacokinetic (PK) portion of the study (days 0-56). Sixty-five patients entered the long-term extension on MR Prograf. Patients were evaluated for MR Prograf dosing and trough levels, laboratory values, concomitant medications,

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graft survival, and adverse events. The mean dose of MR Prograf at conversion was 5.3 mg/day (1-18 mg/day) and was 5.6 mg/day (2-16 mg/day) at one year. At conversion, the mean tacrolimus trough concentration was 6.9 ng/mL (3.2-17.5 ng/mL) and at one year was 6.5 ng/mL (2.0 -11.7 ng/mL). No significant changes in any laboratory parameters were observed during the PK portion of the study and one year follow-up period. Medication use for diabetes, hypertension, and hyperlipidemia were unchanged from conversion to one year. Renal function remained stable. Seven patients discontinued MR Prograf due to adverse events ranging from mild to moderate in intensity, four patients withdrew consent and one patient at her own discretion discontinued MR Prograf. There were no graft losses or deaths. Additionally, the adverse events encountered on MR Prograf in the PK portion of the study and in the one year follow-up are consistent with those reported in the Prograf package insert. Study authors concluded that the one year follow-up confirms the safety and efficacy of mg:mg conversion from Prograf BID to MR Prograf.

#932 A ONE YEAR FOLLOW-UP STUDY OF STABLE LIVER TRANSPLANT RECIPIENTS CONVERTED FROM TWICE DAILY PROGRAF TO ONCE DAILY MODIFIED RELEASE TACROLIMUS. Rita Alloway. May 23, 2005, 2:50 pm, Immunosuppression/Rejection: Liver Transplantation II (2:00 PM-3:30 PM), 6B.

Pediatric Liver Transplant Study Confirms Steady-State PK of MR Prograf®

In a milligram to milligram study designed to evaluate tacrolimus exposure and trough levels in stable pediatric liver transplant recipients converted from Prograf to MR Prograf in a single sequence, the results demonstrated that MR Prograf is equivalent to Prograf. The open label, multi-center study had five participating centers to compare the PK of tacrolimus in 18 stable pediatric liver transplant recipients. Eligible patients were ≤ 12 years of age who had received a liver transplant at least six months prior to enrollment, who were receiving stable doses of Prograf with equal whole milligram (mg) dose in AM and PM for more than two weeks prior to enrollment and who had stable renal function (defined by calculated creatinine clearance >50 mL/min/m² using the Schwartz formula) prior to enrollment. Patients receiving sirolimus therapy or any other drug interfering with tacrolimus metabolism, or experiencing abnormal liver function at screening (defined as AST or ALT $>2x$ the upper limit of normal) or any patient experiencing rejection episodes requiring antilymphocyte antibody therapy in the last six months were excluded from this study. Patients received Prograf BID on Days 1-7. Patients were converted to the same mg-for-mg daily dose of MR Prograf on Day 8. Twenty-four hour PK profiles were obtained on Days 7 and 14. Laboratory and safety parameters were also evaluated. At the

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conclusion of the study, eighteen pediatric patients completed both PK profiles. The ratio of AUC_{0-24} of MR versus Prograf was 100.9% at steady state (Day 14 vs. Day 7) with a 90 percent confidence interval (CI) of (90.8, 112.1). The C_{min} ratio of MR Prograf versus Prograf was 91.8 percent with a 90 percent CI of (82.6, 102.2). C_{min} was highly correlated with AUC_{0-24} for Prograf (Day 7 $r=0.94$) and MR Prograf (Day 14 $r=0.90$). Based on the results, the authors concluded that the steady-state PK of tacrolimus on MR Prograf is equivalent to Prograf after a mg-for-mg conversion in stable pediatric liver transplant recipients. Safety and efficacy are currently being assessed in a long-term study.

#1394 CONVERSION OF STABLE PEDIATRIC LIVER TRANSPLANT RECIPIENTS FROM TWICE DAILY PROGRAF TO ONCE DAILY MODIFIED RELEASE TACROLIMUS.

Thomas G. Heffron. May 24, 2005, 1:20 pm, Mini-Oral Session: Liver: Pediatrics (12:45 PM-1:45 PM), 611-614.

About Prograf®

Prograf® is indicated for the prophylaxis of organ rejection in patients receiving kidney or liver transplant and has been marketed in North America, Europe, and Japan. Worldwide, Prograf® is commercially available in 68 countries. Currently approximately 70% of new kidney transplant recipients take Prograf®. Only experienced physicians and qualified facilities should manage patients prescribed Prograf®. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Insulin dependent post transplant diabetes occurred in up to 20% of patients but was reversible in some patients. Black and Hispanic kidney transplant patients were at an increased risk. Common adverse reactions are nephrotoxicity, neurotoxicity, gastrointestinal disturbances, hypertension, and infection. Prograf® is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf® injection is contraindicated in patients with a hypersensitivity to castor oil. For full prescribing information, visit www.prograf.com or contact Astellas at 1-800-727-7003. Visit www.transplantlife.com for free educational information related to transplantation.

About Astellas

Astellas Pharma US, Inc. is a subsidiary of Astellas Pharma Inc., located in Tokyo, a pharmaceutical company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. In April 2005, the company was formed through the merger of Fujisawa Pharmaceutical Co., Ltd. and Yamanouchi Pharmaceutical Co., Ltd. The organization is committed to becoming a global mega pharmaceutical company by combining outstanding R&D and marketing capabilities and continuing to grow in the world pharmaceutical market.

*The American Heart Association Web site, www.americanheart.org, "Considerations When Prescribing Medication": <http://www.americanheart.org/presenter.jhtml?identifier=81>.

**Richter A, Anton SE, Koch...The impact of reducing dose frequency on health outcomes, *Clin Ther* 2003, Aug 25 (8) 2307-35. Rudd P, Partial Compliance: implications for clinical practice. *J Cardiovascular Pharmacology* 1993, 22, Suppl A:S1-5.

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