Summary of Results for Laypersons

What was the Study Called?

A Multicenter, Randomized, Open Clinical Study to Compare the Efficacy and Safety of a Combination of Tacrolimus With Sirolimus Versus a Tacrolimus/Mycophenolate Mofetil Based Regimen in Kidney Transplantation. This study was also called the TERRA study.

Why was this Study Needed?

Tacrolimus, sirolimus, mycophenolate mofetil (MMF) and steroids are medicines that are used to lower a patient's immune system after an organ transplant. The immune system is part of the body that fights foreign objects or infections. Following organ transplant, the body recognizes the new organ as a foreign object. Medicines that lower a patient's immune system help prevent the body from rejecting the new organ. These 4 medicines have been used to prevent rejection after kidney transplant.

When a patient is treated with more than 1 medicine, it is referred to as a "treatment regimen." At the time of the study, tacrolimus was approved in the United States, Japan and Europe. It was approved to be used as the primary medicine to prevent rejection and also to be used after rejection starts for both liver and kidney transplants. Sirolimus and MMF were approved in the United States and Europe to be used in combination with another medicine to prevent rejection. The use of steroids to prevent and treat rejection was routine and well established.

Sirolimus had been shown to be safe and effective when used together with tacrolimus. However, the best dose of sirolimus had not yet been shown. This study was designed to verify that neither a high nor a low dose sirolimus regimen was less effective at preventing rejection than an established MMF regimen. For any treatment regimen proven to be comparable, the study was also designed to determine if it was actually better than the MMF regimen. The two sirolimus doses tested were 0.5 mg daily and 2.0 mg daily.

The main objective of this study was to compare 3 treatment regimens which could be used to prevent rejection for adult kidney transplant patients. The 3 treatment regimens were:

- Low dose sirolimus regimen: Tacrolimus + 0.5 mg daily sirolimus + steroid
- High dose sirolimus regimen: Tacrolimus + 2.0 mg daily sirolimus + steroid
- MMF regimen: Tacrolimus + 1.0 g daily MMF + steroid

This study took place at 75 clinics in 16 countries which included: Austria, Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Great Britain, Hungary, Italy, Netherlands, Poland, Spain, Sweden and Switzerland. The study started in May 2002 and ended in September 2003. The sponsor (Astellas) reviewed all the study information and created a report of the results. This is a summary of that report.

What Kind of Study was This and Who Took Part in it?

This study was based on a noninferiority design. A noninferiority study is one that compares one treatment (usually a new treatment) to another treatment (usually an established treatment) with the aim of showing that the new treatment regimen is not worse than the established treatment regimen, with regard to the primary question being addressed.

This was an "open-label" study which means that both the doctor and the patient knew which treatment the patient was getting.

Patients were randomly assigned to 1 of the 3 regimens. The study lasted 6 months and started right after kidney transplant surgery. During the 6 months the patients had 7 clinic visits.

Patients were 18 years and older and had been diagnosed with end stage kidney disease.

A total of 995 patients were assigned to 1 of the treatment regimens. Patients were assigned as follows:

- Low dose sirolimus regimen: 325 patients
- High dose sirolimus regimen: 325 patients
- MMF regimen: 327 patients

A total of 977 patients took at least 1 dose of study medicine.

	Number of Patients
Age Group Aged 18 years and older	 977
Men Women	624 353
EU Countries Outside EU	941 36

What Were the Study Results?

The study showed that the high dose sirolimus regimen was not less effective than the MMF regimen at preventing rejection. The study did not, however, show that the high dose sirolimus regimen was any better than the MMF regimen with regard to preventing transplant rejection.

The study was unable to show that the low dose sirolimus regimen was less effective than either the MMF regimen or the high dose sirolimus regimen. Although the low dose sirolimus regimen was determined to be less effective at preventing transplant rejection than the high dose sirolimus regimen, it could not be absolutely determined that it was indeed, less effective than MMF.

What Adverse Reactions did Patients Have?

A lot of research is needed to know whether a medicine causes a medical problem. So when new medicines are being studied researchers keep track of all medical problems that patients have while they are in the study. These medical problems are called "adverse events" and are recorded whether or not they might be caused by the treatment taken. An "adverse reaction" is any medical problem or "adverse event" that is judged by the study doctor to be possibly caused by a medicine or treatment used in the study.

The table below shows the most common adverse reactions experienced by patients while taking part in this study. Information from 977 patients who received at least 1 dose of study medicine is included in the table below.

Adverse Reactions	Tacrolimus + 0.5 mg daily Sirolimus + Steroid (out of 325 patients)	Tacrolimus + 2.0 mg daily Sirolimus + Steroid (out of 325 patients)	Tacrolimus + 1.0 g daily MMF + Steroid (out of 327 patients)
Increased amounts of fat and fatty substances in the blood	54	70	24
Diabetes	17	45	31
Diarrhea	17	23	44
Urinary tract infection	30	39	42
Increased blood level of cholesterol	16	40	12
Increased blood sugar level	17	35	20

Overall the patients who were in one of the groups receiving sirolimus were more likely to have increased cholesterol levels.

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or needs hospital care. Some people had serious adverse reactions: 76 patients in the low dose sirolimus regimen, 108 patients in the high dose sirolimus regimen and 69 patients in the MMF regimen.

A total of 21 patients died, 7 in each of the treatment groups. Of these, 2 in the low dose sirolimus group, 3 in the high dose sirolimus group and 2 in the MMF group died after withdrawal. Of note, 1 of the criteria for inclusion in this study was for the patient to have end stage kidney disease.

Where Can I Learn More About This Study?

Astellas might perform additional trials to better understand tacrolimus combination treatment.

This summary of the clinical study results is available online at http://www.astellasclinicalstudyresults.com. Please remember that researchers look at the results of many studies to find out how well medicines work and which adverse reactions they might cause. If you have questions about tacrolimus combination treatment, please discuss these with your doctor.

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