Summary of Results for Laypersons

What was the Study Called?

A Multicenter, Four Arm, Randomized, Open Label Clinical Study Investigating Optimized Dosing in a Prograf®-/Advagraf®-Based Immunosuppressive Regimen in Kidney Transplant Subjects. This study was also called the OSAKA study.

Why was this Study Needed?

Advagraf (also known as tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL®, FK506E, MR4, or tacrolimus modified-release) is a prescription medicine that is 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. Without medication, the body's immune system would fight the new organ, resulting in rejection of the new organ. In addition, the body's immune system could decrease the ability of the new of the new organ to work (i.e., organ dysfunction), or prevent the new organ from working at all (i.e., graft loss).

There are other medicines besides Advagraf that lower the immune system. Different combinations and doses of these medicines have been tested in the past to lower the immune system. When a patient is treated with more than 1 medicine, it is referred to as a "treatment regimen." This study was done to verify that the 3 Advagraf regimens were not meaningfully less effective than an established Prograf regimen with regard to preventing the immune system from damaging the kidney (as manifested by rejection, kidney dysfunction, or graft loss). For Advagraf regimens that were proven not to be less effective than the established Prograf regimen, the study was also designed to determine if they were actually better than the Prograf regimen. The other medicines used in this study are commonly given to patients who have organ transplant surgery. In this study, the 4 treatment regimens were:

- Regimen 1: 0.1 mg/kg Prograf twice daily + mycophenolate mofetil (MMF) + corticosteroids for 24 weeks
- Regimen 2: 0.2 mg/kg Advagraf daily + MMF + corticosteroids for 24 weeks
- Regimen 3: 0.3 mg/kg Advagraf daily + MMF + corticosteroids for 24 weeks
- Regimen 4: 0.2 mg/kg Advagraf daily + MMF + basiliximab + corticosteroids 1 dose only

Regimen 1 was considered the reference regimen for this study. The "reference" regimen refers to the current standard therapy given to patients having a kidney transplant. Regimens 2, 3 and 4 were compared to regimen 1. In regimen 4 corticosteroids were only given to the patient before, during or after surgery. In regimens 1, 2 and 3 corticosteroids were given to the patient after surgery and also daily for the 24 weeks of the study.

To ensure that patients were dosed with an amount of Advagraf to prevent organ rejection but not so much as to cause unwanted or adverse effects (i.e., adverse reactions), patients were to have a periodic blood sample drawn just prior to taking Advagraf in order to measure the

amount of tacrolimus in the blood. Following the initial dose of Advagraf, the dose of all regimens was to be adjusted as needed.

The main question to be answered in this study was whether each Advagraf regimen (regimens 2, 3, and 4), was unacceptably less effective (i.e., inferior) than the Prograf regimen at preventing the immune system from damaging the transplanted kidney via rejection, graft loss or graft dysfunction. If it was shown that the Advagraf regimen was not less effective to the Prograf regimen, the study could also help answer the question of whether or not the Advagraf regimen was actually better than the Prograf regimen.

The study took place at 110 clinics in 22 countries worldwide which included: Argentina, Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Switzerland and the United Kingdom. The study took place from May 2008 to March 2010. When the study ended, the sponsor (Astellas Pharma Europe Ltd) 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 non-inferiority study design. A non-inferiority study is one that compares a novel treatment (i.e., regimens 2, 3, and 4) to an established treatment (i.e., regimen 1) with the aim of showing that the new treatment regimen is not unacceptably worse (inferior) than the established treatment regimen, with regard to the primary question being addressed.

This was an "open-label" study. Open-label means that the patients knew which treatment regimen they received. Both men and women took part in this study. They were all over 18 years old. They all had kidney transplant surgery. Patients were randomly assigned to 1 of the 4 regimens by chance alone. An equal number of patients were assigned to each of the 4 regimens. Care was taken to make sure that there was an equal number of patients 60 years and over in all 4 regimens.

The study lasted 24 weeks. During the study patients were seen and assessed 7 times (visits).

A total of 1251 patients enrolled in the study. A total of 1214 patients were scheduled to receive a kidney transplant and study medicine. Patients were assigned to the treatment regimens as follows:

- Regimen 1: 311 patients
- Regimen 2: 309 patients
- Regimen 3: 307 patients
- Regimen 4: 287 patients

Sixteen subjects either did not have a kidney transplant or did not receive study medicine to which they were randomized. So, a total of 1198 patients had kidney transplant surgery and received at least 1 dose of study medicine.

	Number of Patients (out of 1198)
Age Group	
18 to 59 years	873
Aged 60 years or older	325
Men	806
Women	392
	Number of Patients (out of 1214)
EU Countries	1140
Outside EU	74

What Were the Study Results?

There were 222 patients that violated the study procedures/rules in major ways; therefore, only the 976 patients without the major violations were considered when comparing the regimens for effectiveness at preventing the immune system from damaging the transplanted kidney.

The study showed that Advagraf regimen 2 was not significantly less effective than the Prograf regimen at preventing the immune system from damaging the transplanted kidney. The study did not, however, show that regimen 2 was any better than the Prograf regimen with regard to preventing the immune system from damaging the kidney.

The study was unable to show that Advagraf regimens 3 and 4 were not worse than the Prograf regimen, meaning that the degree to which these Advagraf regimens prevent the immune system from damaging the transplanted kidney could possibly be less effective to that of the Prograf regimen.

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 1214 patients who were scheduled to receive a kidney transplant and study medicine is included.

Adverse Reactions	Regimen 1 (out of 311 patients)	Regimen 2 (out of 309 patients)	Regimen 3 (out of 307 patients)	Regimen 4 (out of 287 patients)
Increased blood sugar level	22	26	28	25
Diabetes	20	15	14	8
High blood levels of fatty substances	18	9	10	6
Urinary tract infection	27	24	26	33
Cytomegalovirus infection (a common viral infection similar to herpes viruses)	21	12	17	9
Kidney damage caused by the effects of a toxin	11	10	16	23
Kidneys not working well	12	12	19	9
Uncontrolled trembling or shaking movements in one or more parts of your body	32	33	26	26
Increase blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	23	26	16	14
Kidney transplant rejection (when the patient's body attacks the new kidney)	25	24	30	26
Diarrhea	17	11	16	10
High blood pressure	15	21	10	12

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care. A total of 315 patients had serious adverse reactions: 72 patients in regimen 1, 81 patients in regimen 2, 79 patients in regimen 3 and 83 patients in regimen 4.

Patients enrolled in this study had end-stage kidney disease and were very sick. During the study a total of 24 deaths were reported. There was no difference across the treatment regimens in rates of deaths. Two deaths were judged by the investigator to be possibly related to study medicine.

Where Can I Learn More About This Study?

Astellas might perform additional trials to better understand Advagraf.

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 Advagraf, please discuss these with your doctor.

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