Summary of Results for Laypersons

What was the Study Called?

A Multicenter, Three Arm, Randomized, Open Label Clinical Study to Compare Renal Function in Liver Transplant Recipients Receiving an Immunosuppressive Regimen of Advagraf® (Immediately or Delayed Post-transplant) and MMF with or without a Monoclonal Anti-IL2R Antibody (Basiliximab). This was also called the DIAMOND 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.

There are other medicines besides Advagraf that lower the immune system. All of these medicines can have an effect on the patient's kidneys. This study was done to find out if varying the exposure (e.g., dose) to Advagraf affects the kidneys. All patients in this study received treatment with Advagraf after they had liver transplant surgery. When a patient is treated with more than 1 medicine, it is referred to as a "treatment regimen." The other medicines used in this study are commonly given to patients who have organ transplant surgery. In this study, 3 treatment regimens containing Advagraf were tested. All patients received MMF (mycophenolate mofetil) and a single dose of corticosteroids. In addition, they received one of the following 3 treatment regimens:

- Regimen 1: 0.2 mg/kg Advagraf (taken daily starting within 18 hours after transplant surgery)
- Regimen 2: 0.15 mg/kg Advagraf (taken daily starting within 18 hours after transplant surgery) + basiliximab
- Regimen 3: 0.2 mg/kg Advagraf (taken daily starting 5 days after transplant surgery) + basiliximab

Regimen 1 was considered the reference regimen for this study. Thus regimen 2 and regimen 3 were each compared to regimen 1. Regimen 2 (lower Advagraf initial dose) tested whether a lower initial dose of Advagraf (0.15 mg/kg) was better for the kidneys than regimen 1. Regimen 3 (delayed Advagraf administration) tested whether delaying the initial dose of Advagraf for 5 days after surgery was better for the kidneys than regimen 1. The lower dose in regimen 2 and the delayed dose in regimen 3 were in combination with basiliximab to provide additional protection from rejection in the early post-transplant period. All patients received Advagraf once daily for up to 24 weeks. 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.

After patients recovered from surgery, the range of acceptable levels of tacrolimus in the blood was slightly lower for regimen 2 than for regimen 1 and slightly lower for regimen 3 than for regimen 2.

The main question this study helped to answer was whether varying the exposure (e.g., dose) to Advagraf, compared to the standard (regimen 1) way of exposing patients, affected the kidneys. The treatment regimens tested were lower Advagraf initial dose (regimen 2) and delayed Advagraf administration (regimen 3). Also, it was important to find out what unwanted effects might occur.

The study took place at 72 clinics in 23 countries worldwide which included: Argentina, Austria, Belarus, Belgium, Brazil, Canada, Colombia, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, Mexico, Poland, Romania, Russian Federation, South Africa, Spain, Sweden, Switzerland, and the United Kingdom. The study took place from September 2009 to January 2013. 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) to an established treatment (i.e., regimen 1) 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. 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 liver transplant surgery. Patients were randomly assigned to 1 of the 3 regimens. Since infection with hepatitis C can have a negative effect on the liver, patients with hepatitis C were assigned to treatment regimens so that each regimen had a similar number of patients with hepatitis C. An equal number of patients were assigned to each of the 3 regimens.

The study lasted 24 weeks. During the study patients made eight clinic visits.

The first day of the study was on the day of liver transplant surgery. In treatment regimens 1 and 2, Advagraf was given to patients in the morning following their liver transplant surgery. In treatment regimen 3, the first dose of Advagraf was given in the morning 5 days after liver transplant surgery.

A total of 901 patients volunteered to be in the study. A total of 893 patients enrolled in the study. A total of 857 patients had liver transplant surgery and received at least 1 dose of study medicine. The patients were assigned to the regimens as follows:

- Regimen 1: 289 patients
- Regimen 2: 291 patients
- Regimen 3: 277 patients

Information for the patients who had a liver transplant and received at least 1 dose of study medicine is in the table below.

	Number of Patients
Age Group	
Aged 18 to 49 years	231
Aged 50 to 65 years	552
Aged 66 to 75 years	73
Age Unknown	1
Men	604
Women	252
EU Countries	720
Outside EU	137

What Were the Study Results?

Patients who received a lower Advagraf initial dose (regimen 2) or a delayed Advagraf administration (regimen 3) had better kidney function compared to patients who received treatment regimen 1. Taking Advagraf in this study was well tolerated.

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 857 patients who took at least 1 dose of study drug is included below.

Adverse Reactions	**Regimen 1 (out of 289 patients)**	**Regimen 2 (out of 291 patients)**	**Regimen 3 (out of 277 patients)**	**Total (out of 857 patients)**
Kidney failure	56	46	34	136
Kidneys not working well	19	23	16	58
Sudden onset of kidney failure	22	13	14	49
Kidney damage caused by the effects of a toxin	11	8	4	23
Cytomegalovirus infection (a common viral infection similar to herpes viruses)	16	9	11	36
Pneumonia	9	12	6	27
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Adverse Reactions	Regimen 1 (out of 289 patients)	Regimen 2 (out of 291 patients)	Regimen 3 (out of 277 patients)	Total (out of 857 patients)
Uncontrolled trembling or shaking movements in one or more parts of your body	29	27	27	83
Headache or head pain	13	7	3	23
Diarrhea	37	46	33	116
Nausea or urge to vomit	18	12	10	40
Decreased number of white blood cells	19	26	26	71
Lack of enough red blood cells	17	10	16	43
Decreased number of platelets (platelets are blood cells that help blood clot)	15	8	9	32
Shortage of all types of blood cells	11	5	3	19
Increased blood sugar level	23	22	7	52
Increased blood level of potassium	16	12	10	38
Increase blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	17	14	20	51
High blood pressure	26	39	23	88
Liver transplant rejection (when the patient's body attacks the new liver)	23	15	19	57
Fever	8	11	8	27
Itching	3	9	8	20
Stoppage or slowing of the flow of bile from the liver	4	13	6	23

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems, or needs hospital care. A total of 252 patients had serious adverse reactions: 88 patients in regimen 1, 89 patients in regimen 2 and 75 patients in regimen 3.

Patients enrolled in this study had end-stage liver disease and were very sick. The death rate is high in this patient population. Out of 857 patients enrolled in this study, a total of 89 deaths were reported; 1death was judged by the investigator to be probably related to study medicine and 14 deaths were judged 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.

Sponsor contact details:

Astellas Pharma Europe, Ltd
2000 Hillswood Drive
Chertsey, Surrey, KT16 0RS
United Kingdom