Summary of Results for Laypersons

What was the Study Called?

A Phase IV, Randomized, Open-Label, Comparative, Multi-Center Study to Assess the Safety and Efficacy of Advagraf® (Modified Release Tacrolimus, once daily) after using Prograf® (Tacrolimus twice daily) in de novo Liver Transplant Recipients

Why was this Study Needed?

The immune system is part of the body that fights foreign objects or infections. After organ transplantation, the immune system recognizes the new organ as a foreign object. Tacrolimus is a medicine that reduces the strength of the immune system. It prevents the body from rejecting organ transplants. Tacrolimus comes in capsules to be taken by mouth (orally). Prograf (also known as FK506, immediate-release tacrolimus, Adoport, Capexion, Vivadex, Tacni, Tacniteva and Tacni-transplant) capsules are taken twice a day. Advagraf (also known as Graceptor, tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL, FK506E, MR4 or tacrolimus modified-release) capsules are easier for patients because they are taken once a day.

The main question this study helped answer was if Advagraf was the same as Prograf in helping transplanted livers survive longer than 24 weeks. Since most of the Advagraf studies have been conducted in Western countries, there was a need to study Advagraf in Korean patients. It was also important to find out what unwanted effects these patients had from Advagraf.

This study took place at 4 hospitals in the South Korea. The study started in January 2013 and ended in January 2017. When the study ended, 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 was an "open-label" study. This means that all patients knew which of the 2 study medicines they took, Prograf or Advagraf.

Men and women aged 20 to 65 years could take part in the study if:

- They received a liver transplant from a living donor or a donor who had completely lost brain function (brain dead donor).
- They needed the liver transplant because of end-stage liver failure.
- Women were not pregnant at study start. They did not plan to become pregnant during the study. Women who could have children used reliable birth control methods during the study.

Patients could not take part in this study if:

- They had previously received another organ transplant or required a repeated liver transplant.

- They had received an auxiliary transplant (a partial left or right lobe liver transplant that acts as temporary support for the patient's liver) or used an bioartificial liver (an artificial support device that temporarily replaces liver functions for a patient until a liver transplant is possible).
- Before the transplant, they had a condition for which they needed a medicine that reduced the strength of the immune system. (Patients were allowed to receive treatment to reduce the strength of their immune system for a liver disorder as long as it was for less than 1 month prior to the liver transplant. However, patients had to stop taking it just before the transplant.)
- Before the transplant, they had cancer or needed anticancer medicines that were given to them via a vein or the mouth. It was acceptable if they had skin cancer that was cured.
- They had severe diarrhea, vomiting, active sore (ulcer) in the lining of the stomach or any other stomach disorder that would make it hard for enough amount of the tacrolimus medicine to reach the blood.
- They suffered from any type of substance abuse, psychological disorder or communication disorder.
- They had human immunodeficiency virus (HIV).

During the study, the study doctor did a check-up of the patients at several study visits. At visit 1, patients were checked to see if they could be in the study. Blood samples were also collected during this visit. The prescribing information for Advagraf in Korea states that the initial dosage for patients with a liver transplant is to be 0.1 to 0.2 mg per kg of body weight. Advagraf has the same starting daily dose as Prograf, but Advagraf is taken once a day and Prograf is taken twice a day. Over 24 hours, blood levels of tacrolimus need to stay high enough to prevent transplant rejection. A patient's dose of tacrolimus can be adjusted based on a patient's symptoms and guided by the patient's blood concentration of tacrolimus right before the next dose of Advagraf or Prograf ("trough level of tacrolimus"). During this study, the target dose of the study medicine was 0.1 to 0.2 mg per kg body weight per day.

Patients who could be in the study received 2 doses of Prograf capsules before the liver transplant surgery or within 3 days after the liver transplant surgery. Patients were picked to receive 1 of 2 treatments by chance alone:

- Advagraf: After the transplant surgery, the patients took Prograf twice a day for 4 weeks. After 4 weeks, the patients took Advagraf capsules once a day until week 24.
- Prograf: After the transplant surgery, the patients continued to take Prograf capsules twice a day until week 24.

At each visit, the study doctor checked for symptoms of transplant rejection. The clinic staff took blood samples to check the amount of tacrolimus in the blood. The study doctor adjusted the Prograf or Advagraf doses based on the specific needs of the patient.

A total of 32 patients were in the study and took at least 1 dose of Prograf or Advagraf:

- 15 patients took Prograf
- 17 patients took Advagraf

	Number of Patients	
	Prograf	**Advagraf**
Age Group Aged between 33 and 65 years	15	17
Sex Men Women	11 4	11 6
Hospital Location South Korea	15	17

What Were the Study Results?

The main question this study helped answer was if Advagraf was the same as Prograf in helping transplanted livers survive longer than 24 weeks. To answer this question, the study looked at the change in the percentage of patients with liver transplant rejection in the Advagraf group compared to that in the Prograf group. As a rule, liver transplant rejection with Advagraf and Prograf was considered similar if the change was < 30% at week 24. The results from the study showed that the survival of the transplanted liver was the same for Advagraf and Prograf after 24 weeks. The change in liver transplant rejection with Advagraf and Prograf was similar (between -6.35% and 20.63%). One patient in the Advagraf group had a transplant rejection and no patients in Prograf group had a transplant rejection.

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 adverse reactions experienced by patients who took at least 1 dose of study medication.

Adverse Reaction	Prograf Group (out of 15 patients)	Advagraf Group (out of 17 patients)
Heartburn	1 (6.7%)	0
Narrowing of the bile ducts	0	1 (5.9%)
Infection caused by the cytomegalovirus (CMV)	0	2 (11.8%)
Increased blood level of a liver enzyme (alanine aminotransferase, ALT/SGPT)	1 (6.7%)	0
Increased blood level of a liver enzyme (aspartate aminotransferase, AST/SGOT)	1 (6.7%)	0
Increased blood level of a liver pigment (bilirubin) often a sign of liver problems	0	1 (5.9%)
Leg and/or arm pain	0	1 (5.9%)
Hair loss	0	1 (5.9%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care and is judged by the study doctor to be possibly caused by a medicine or treatment used in the study.

Three patients experienced serious adverse reactions. In the Prograf group, 1 patient experienced increased blood levels of the liver enzymes alanine aminotransferase (ALT/SGPT) and aspartate aminotransferase (AST/SGOT). In the Advagraf group, 1 patient experienced narrowing of the bile ducts and 1 patient experienced infection caused by the cytomegalovirus (also known as CMV which is a virus that can be spread to anyone and can cause problems in people whose immune system does not work well).

One patient in the Advagraf group died. This death was not related to the study medicine.

Where Can I Learn More About This Study?

The information in this document reflects the information available as of December 2017.

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 Prograf or Advagraf, please discuss these with your doctor.

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