Summary of Results for Laypersons

What was the Study Called?

A Phase 2, Parallel Group, Randomized, Multicenter, Open-label Study to Compare the Pharmacokinetics of Tacrolimus in De Novo Pediatric Allograft Recipients Treated with an Advagraf® or Prograf® Based Immunosuppressive Regimen, Including a Long-term Follow-up.

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. Prograf (also known as FK506 and immediate-release tacrolimus) comes in capsules taken by mouth twice a day. Prograf is approved for all patients with organ transplants.

Advagraf (also known as Graceptor, tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL, FK506E, MR4 or tacrolimus modified-release) capsules are taken once a day. Because patients only need to take Advagraf in the morning, it may be easier for some to remember to take it. At the time of this study, Advagraf was approved for adults (at least 18 years old) with organ transplants. Advagraf was not approved for children and teenagers with organ transplants. Therefore, there was a need to study Advagraf in children and teenagers who had received an organ transplant.

This study was conducted in children and teenagers who had received a single organ transplant. This study had 3 parts: A, B and C.

Part A started 1 to 4 days after the transplant surgery and lasted 4 weeks. In part A, patients took either Prograf twice daily or Advagraf once daily for 4 weeks. Part A of the study looked at the amount of tacrolimus (as either Advagraf or Prograf) that reached the blood over 24 hours after the first dose and after 7 and 28 days. Part A answered the question if these amounts were similar with Prograf twice daily and with Advagraf once daily.

Part B started at the end of part A and continued until 1 year after the transplant surgery. In part B, patients continued taking the same study medicine that they took during part A. Part B of the study looked at the features of transplant rejection by the body and at the survival of patients and transplants. And part B looked at patients who stopped taking study medicine prematurely. Part B of the study answered the question how effective Advagraf once daily was compared to Prograf twice daily. It was also important to find out what unwanted effects patients had from the study medicines.

For patients who were at least 18 years old and lived in countries where Advagraf was approved, the study ended at the end of part B. At the end of part B, the study doctor asked those patients to obtain Advagraf via their local pharmacy. Patients who were younger than 18 years and/or lived in countries where Advagraf was not approved could enroll in part C of

the study. In Part C, they could continue taking Advagraf under the supervision of their doctor. Part C ended when patients stopped taking Advagraf; or when patients who lived in countries where Advagraf was approved turned 18 years. The latter patients were asked to obtain Advagraf via their local pharmacy.

This study took place at 8 clinics in Czech Republic, France, Italy, Poland and the UK. The study started in April 2012. Part B of the study ended in May 2017. When part B of the study ended, the sponsor (Astellas) reviewed all of the study information and created reports for parts A and B. This is a summary of those reports.

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 study medicine they took, Prograf or Advagraf.

Children and teenagers could take part in the study if:

- They were younger than 16 years.
- They received a liver, kidney or heart transplant.
- Female patients were not pregnant.
- Male and female patients who were sexually active used reliable birth control methods.
- They were able to swallow whole Prograf or Advagraf capsules.

Patients could not take part in the study if:

- They had received a transplant of more than 1 organ. Or they had received another organ transplant in the past.
- They had high pulmonary vascular resistance, which did not change in response to treatment. This type of resistance occurs when the lung artery creates resistance against the blood flowing into it from the heart's right ventricle. It is normal to have low pulmonary vascular resistance.
- They had cancer within the last 5 years. It was acceptable if they had skin cancer that was cured. It also was acceptable if the cancer was in the organ for which they received a transplant.
- They had a medical condition that could make it hard for enough study medicine to reach the blood. For example, they had severe diarrhea or vomiting.
- They had a condition for which they needed a medicine that reduced the strength of the immune system. The condition was different from their organ transplant.

Patients with a liver or heart transplant could not take part in the study if:

- Their kidneys did not work well. This meant that the level of their blood creatinine before the transplantation was too high. Creatinine is a substance that is normally removed by the kidneys into the urine.

Patients with a kidney or heart transplant could not take part in the study if:

- They had significant liver disease. This meant blood levels of certain liver chemicals were 3 times higher than normal during the month before the transplantation. High blood levels of liver chemicals result when those chemicals leak from damaged liver cells into the blood.

During part A of the study, the study doctor did a check-up of the patients at baseline and 6 study visits. Baseline was the period of time before the skin was closed as part of the patient's transplant surgery. At baseline, patients were checked to see if they could be in the study. Visit 1 was 1 to 3 days later. At visit 1 (day 1), patients with a heart transplant were checked to see if they could remain in the study. They could remain in the study if their stomach worked normally and their kidneys worked sufficiently.

All patients who could be in the study were picked for 1 of 2 treatments by chance alone:

- Prograf: Patients were to take the first dose in the morning 1 to 3 days after their transplant surgery. Patients who had received a heart transplant were to take 0.0375 mg/kg twice daily by mouth (orally). All other patients were to take 0.15 mg/kg orally twice daily. After the first dose, the study doctor was allowed to adjust the dose to get the right amount of tacrolimus in the blood.
- Advagraf: Patients were to take the first dose in the morning 1 to 3 days after their transplant surgery. Patients who had received a heart transplant were to take 0.075 mg/kg orally once daily. All other patients were to take 0.3 mg/kg orally twice daily. After the first dose, the study doctor was allowed to adjust the dose to get the right amount of tacrolimus in the blood.

At visits 1 (day 1), 4 (day 7) and 6 (day 28), the clinic staff took a total of 11 blood samples to measure the amount of tacrolimus in the blood. The clinic staff took 1 sample right before the patients took their morning dose of study medicine. During the 24 hours after the morning dose, the clinic staff took the remaining 10 blood samples.

During part B of the study, the study doctor did a check-up of the patients at 4 study visits (2, 3 and 6 months and 1 year after visit 1 in part A of the study). Patients continued taking the same study medicine that they took during part A. 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 dose of study medicine based on the specific needs of the patient.

A total of 44 patients were in part A of the study and took at least 1 dose of study medicine. All 44 patients were in parts A and/or B of the study and took at least 1 dose of study medicine.

- 24 patients took at least 1 dose of Prograf in part A.
- 20 patients took at least 1 dose of Advagraf in part A.
- 24 patients took at least 1 dose of Prograf in parts A and/or B.
- 20 patients took at least 1 dose of Advagraf in parts A and B.

	Number of Patients in Part A and in Parts A and B (out of 44 patients)
Age Group	
Aged 2 to 11 years	24
Aged 12 to 16 years	20
Sex	
Boys	33
Girls	11
Clinic Location	
European Union Countries	44
Czech Republic	10
France	6
Italy	7
Poland	7
The UK	14
Outside European Union	0

What Were the Study Results?

This study was conducted in children and teenagers who had received a single organ transplant. They took either Prograf twice daily or Advagraf once daily. The study had 3 parts: A, B and C. Part A started 1 to 4 days after the transplant surgery and lasted 4 weeks. Part B started at the end of part A and continued until 1 year after the transplant surgery. (The results of part C are not reported here because part C is ongoing.)

Part A of the study looked at the amount of tacrolimus (as either Advagraf or Prograf) that reached the blood over 24 hours after the first dose and after 7 and 28 days. As a rule, the amounts are considered similar if the estimated amount of Advagraf in the blood is between 80% and 125% of that with Prograf.

The results from part A were that the estimated average amount of Advagraf in the blood was:

- between 46% and 95% of that with Prograf after the first dose;
- between 71% and 120% of that with Prograf after 7 days;
- between 81% and 124% of that with Prograf after 28 days.

Part A showed that the amount of tacrolimus (as either Advagraf or Prograf) in the blood was similar after 28 days.

Part B of the study looked at the number of patients that had symptoms of transplant rejection by the body and at the survival of patients and transplants. And part B looked at patients who stopped taking study medicine prematurely.

The results from parts A and B were that 5 patients had symptoms of transplant rejection on 1 occasion. These symptoms were confirmed by studying samples of the transplants ("biopsies") under the microscope. Four of the 5 patients were in the Prograf group and the fifth patient was in the Advagraf group. No patients died. All transplants survived 1 year

after the transplant surgery. Three patients stopped taking Prograf prematurely. These patients did not return to the clinic for a further check-up, so it was unknown what happened to their transplant.

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.

During part A of the study, 15 patients (7 Prograf, 8 Advagraf) experienced adverse reactions while taking study medicine.

During parts A and B of the study, 29 patients (15 Prograf, 14 Advagraf) experienced adverse reactions while taking study medicine.

The table below shows the adverse reactions experienced by at least 3 patients who took at least 1 dose of study medicine in part A or in parts A and B of the study. These were the common adverse reactions.

During part A, 3 patients who took Prograf and 1 patient who took Advagraf had high blood pressure. Three patients who took Prograf had Epstein-Barr virus in their blood. This did not occur in any of the patients who took Advagraf. Each of the other adverse reactions occurred in 1 or none of the patients who took Prograf and in 2 or fewer patients who took Advagraf.

Three common adverse reactions were experienced by more patients during parts A and B than during part A.

- Two patients who took Prograf and 5 patients who took Advagraf had increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine).
- Four patients who took Prograf and 2 patients who took Advagraf had diarrhea.
- Four patients who took Prograf and 1 patient who took Advagraf had infection of the upper respiratory tract (nose, sinuses, throat, wind pipe and voice box).

Adverse Reaction	Part A Prograf (out of 24 patients)	Part A Advagraf (out of 20 patients)	Parts A and B Prograf (out of 24 patients)	Parts A and B Advagraf (out of 20 patients)
Any adverse reaction	7 (29.2%)	8 (40.0%)	15 (62.5%)	14 (70.0%)
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	1 (4.2%)	1 (5.0%)	2 (8.3%)	5 (25.0%)
Diarrhea	1 (4.2%)	1 (5.0%)	4 (16.7%)	2 (10.0%)
Infection of the upper respiratory tract (nose, sinuses, throat, wind pipe and voice box)	0	0	4 (16.7%)	1 (5.0%)
High blood pressure	3 (12.5%)	1 (5.0%)	3 (12.5%)	1 (5.0%)
Belly pain	1 (4.2%)	0	2 (8.3%)	1 (5.0%)
Lack of enough red blood cells (anemia)	0	1 (5.0%)	1 (4.2%)	2 (10.0%)
Increased blood level of urea (a waste product that is formed after the liver breaks down proteins)	1 (4.2%)	1 (5.0%)	2 (8.3%)	1 (5.0%)
Cytomegalovirus present in the blood	0	0	1 (4.2%)	2 (10.0%)
Epstein-Barr virus present in the blood	3 (12.5%)	0	3 (12.5%)	0
Increased blood level of medicine that reduces the strength of the immune system	1 (4.2%)	2 (10.0%)	1 (4.2%)	2 (10.0%)

An adverse reaction is considered “serious” when it is life-threatening, causes lasting problems or needs hospital care.

During part A of the study, 6 patients (2 Prograf, 4 Advagraf) who took at least 1 dose of study medicine experienced serious adverse reactions.

During parts A and B of the study, 19 patients (9 Prograf, 10 Advagraf) experienced serious adverse reactions while taking study medicine.

The table below shows the serious adverse reactions experienced by at least 2 patients who took at least 1 dose of study medicine in part A or in parts A and B of the study.

Serious Adverse Reaction	Part A Prograf (out of 24 patients)	Part A Advagraf (out of 20 patients)	Parts A and B Prograf (out of 24 patients)	Parts A and B Advagraf (out of 20 patients)
Any serious adverse reaction	2 (8.3%)	4 (20.0%)	9 (37.5%)	10 (50.0%)
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	0	1 (5.0%)	1 (4.2%)	5 (25.0%)
Fever	0	0	3 (12.5%)	0
Stomach flu caused by sapovirus	0	0	1 (4.2%)	1 (5.0%)
Kidneys not working well	1 (4.2%)	0	2 (8.3%)	0

Where Can I Learn More About This Study?

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

Astellas may perform additional studies to better understand tacrolimus.

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, please discuss these with your doctor.

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