Summary of Results for Laypersons

What was the Study Called?

A Phase II, Open-label, Multi-center Study to Compare the Pharmacokinetics of Tacrolimus in Stable Pediatric Allograft Recipients Converted from a Prograf® Based Immunosuppressive Regimen to a Tacrolimus Prolonged Release, Advagraf® 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. Tacrolimus comes in capsules to be taken by mouth. The study 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 taken once a day. Advagraf is approved for use by adults with organ transplants, but not yet for use by children and teenagers with organ transplants. 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 lasted for 6 weeks. In part A, patients took Prograf twice daily for 7 days and then took Advagraf once daily for 7 days. Part A of the study looked at the amount of tacrolimus that reached the blood over 24 hours on day 7 after the start of Prograf and Advagraf, respectively. Part A answered the question if that amount was the same with twice daily Prograf as with once daily Advagraf.

Part B lasted 1 year. Part B of the study answered the question how effective Advagraf once daily was in helping transplants survive for 1 year. Part B studied patients who took Advagraf once daily during part A and continued to take the drug during part B. Part B of the study looked at the features of transplant rejection by the body. Part B also looked at the survival of patients and transplants. And part B looked at patients who had to stop taking Advagraf prematurely. It was also important to find out what unwanted effects these patients had from the study medicine.

For patients who lived in countries that sold Advagraf, the study ended 1 year after their participation in part B. Patients who lived in countries who did not sell Advagraf were allowed to enroll in part C of the study so that they could continue taking Advagraf under the supervision of their doctor.

This study took place at 14 clinics in Belgium, Czech Republic, France, Germany, Italy, Poland and the UK. The study started in May 2011. Part B of the study ended in

October 2016. 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 at least 5 years old and were not older than 16 years.
- They had received a single organ transplant within 6 months before study start.
- They were taking Prograf for at least 3 months.
- Female patients were not pregnant.
- Female patients who might become pregnant used reliable birth control methods.
- They were able to swallow intact capsules of study medicine.

Patients could not take part in the study if:

- They had received a transplant of more than 1 organ.
- On 1 occasion within 3 months before study start, they had symptoms that showed their body was rejecting their transplant. Or within 6 months before study start, they had needed antibody treatment for such symptoms. (The antibodies were intended to bind the cells that are involved in the transplant rejection.) Or within 12 months before study start, they had symptoms of transplant rejection on at least 2 occasions.
- The study doctor thought that their transplant was not working properly.
- Within 3 months before study start, they made changes to the medicines that they were taking to reduce the strength of the immune system and prevent transplant rejection. Those changes included replacing a medicine, no longer taking a medicine or starting a new medicine.
- They had a medical condition that could interfere with the study outcome.
- They were infected with hepatitis B virus, hepatitis C virus or human immunodeficiency virus.

During part A of the study, the study doctor did a check-up of the patients at 4 study visits. At visit 1, patients were checked to see if they could be in the study. The patients then took their usual oral dose of Prograf capsules twice daily for 30 days. At visit 2, patients were checked to see if they could remain in the study. Patients could remain in the study if:

- The amount of tacrolimus in their blood was stable as measured on at least 2 occasions during the previous 30 days.
- The study doctor thought that the health of the patients was not going to get worse during the study.

Patients who could be in the study continued to take Prograf capsules twice daily for 7 days. At visit 3, 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 Prograf. During the 24 hours after the morning dose, the clinic staff took the remaining 10 blood samples. After the last blood sample, the patients were switched to once daily Advagraf. The patients took Advagraf capsules once daily for 7 days. At visit 4,

the clinic staff also took a total of 11 blood samples. The clinic staff took 1 sample right before the patients took their daily dose of Advagraf. During the 24 hours after this 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 6 study visits (6, 10, 14, 28, 42 and 54 weeks after visit 2 in part A of the study). 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 Advagraf dose based on the specific needs of the patient.

A total of 81 patients were in part A of the study and took at least 1 dose of Prograf. A total of 79 patients were switched to Advagraf and took at least 1 dose of Advagraf during part B.

	Number of Patients in Part A (out of 81 patients)	Number of Patients in Part B (out of 79 patients)
Age Group		
Aged 2 to 11 years	35	33
Aged 12 to 16 years	46	46
Sex		
Boys	47	45
Girls	34	34
Clinic Location		
European Union	81	79
Countries		
Belgium	1	1
Czech Republic	10	10
France	22	22
Germany	1	1
Italy	4	4
Poland	28	27
The UK	15	14
Outside European Union	0	0

What Were the Study Results?

This study was conducted in children and teenagers who had received a single organ transplant. The study had 3 parts: A, B and C. (The results of part C are not reported here because part C is ongoing.)

Part A lasted for 6 weeks. In part A, patients took Prograf twice daily for 7 days and then took Advagraf once daily for 7 days. Part A of the study looked at the amount of tacrolimus that reached the blood over 24 hours on day 7 after the start of Prograf and Advagraf, respectively. The study compared this amount for Advagraf and Prograf. As a rule, the amounts are considered similar if the amount with Advagraf is between 80% and 125% of that with Prograf.

The finding from part A was that the average amount with Advagraf was 96.66% of that with Prograf. Part A showed that the amounts of tacrolimus in the blood were similar after 7 days of taking either Advagraf (once daily) or Prograf (twice daily). This meant that part B of the study could proceed.

Part B lasted 1 year. Part B studied patients who took Advagraf once daily during both parts A and B. Part B of the study looked at the number of patients that had symptoms of transplant rejection by the body. Part B also looked at the survival of patients and transplants. And part B looked at patients who had to stop taking Advagraf prematurely.

The findings from parts A and B were that 1 patient had symptoms of transplant rejection on 1 occasion. No patients died. All transplants survived. Two patients had medical problems that led to discontinuation of Advagraf.

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 adverse reactions experienced by patients who took at least 1 dose of Prograf in part A of the study. The table below also shows the adverse reactions experienced by patients who took at least 1 dose of Advagraf in parts A and B of the study.

During part A, 2 patients who took Prograf had adverse reactions. One of the 2 patients had cold sores or fever blisters. The other patient experienced an infection in the throat.

During parts A and B, 3 patients had diarrhea. Three patients had cold sores or fever blisters. Each of the other adverse reactions occurred in 2 patients.

Adverse Reaction	Part A Prograf (out of 81 patients)	Parts A and B Advagraf (out of 79 patients)
Cold sores or fever blisters (caused by herpes infection of the mouth area)	1 (1.2%)	3 (3.8%)
Vomiting	0	2 (2.5%)
Increased blood sugar level	0	2 (2.5%)
Infection in the throat	1 (1.2%)	2 (2.5%)
Increased number of white blood cells (leukocytes) in the peripheral blood	0	2 (2.5%)
Diarrhea	0	3 (3.8%)
Short-lasting inflammation (swelling and redness) of the paranasal sinuses, which may or may not be as a result of infection	0	2 (2.5%)
Urinary tract infection (caused by *Escherichia* bacteria)	0	2 (2.5%)
Stomach flu	0	2 (2.5%)
Wart	0	2 (2.5%)
More protein leaking into the urine than usual, often a sign of kidney disease	0	2 (2.5%)
Infection of the upper respiratory tract (nose, sinuses, throat, wind pipe and voice box)	0	2 (2.5%)
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	0	2 (2.5%)

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

None of the patients in part A of the study who took at least 1 dose of Prograf or Advagraf experienced serious adverse reactions.

Ten patients in part B of the study experienced serious adverse reactions while taking Advagraf.

The table below shows these serious adverse reactions.

Serious Adverse Reaction	Advagraf (out of 79 patients)
Diarrhea	1 (1.3%)
Inflammation (swelling and redness) of the small and large bowel	1 (1.3%)
Unwanted effects from study medicine interacting with another medicine	1 (1.3%)
Infection of the bile ducts (tubes that carry bile from the liver to the gallbladder and intestines)	1 (1.3%)
Infection with a common virus (cytomegalovirus)	1 (1.3%)
Urinary tract infection (caused by *Escherichia* bacteria)	2 (2.5%)
Stomach flu	1 (1.3%)
Pocket of pus in the liver	1 (1.3%)
Cold sores or fever blisters (caused by herpes infection of the mouth area)	1 (1.3%)
Infection in 1 or both lungs	1 (1.3%)
Bacterial infection on top of an earlier infection	1 (1.3%)
Increased blood level of medicine that reduces the strength of the immune system	1 (1.3%)
Lung disease	1 (1.3%)

Where Can I Learn More About This Study?

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.

Sponsor contact details:

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