Summary of Results for Laypersons

What was the Study Called?

A Long-term, Open-label, Non-comparative Study to Evaluate the Safety and Efficacy of a Modigraf® Based Immunosuppression Regimen in Paediatric Solid Allograft Recipients. This is also known as the PROGRESSION study.

Why was this Study Needed?

A transplant of a liver, kidney or heart is the best treatment for children whose liver, kidney or heart does not work well. 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. As a result, the transplanted organ will survive longer.

Prograf® (also known as tacrolimus or FK506) is approved for use in some patients with organ transplants. Prograf comes in capsules taken by mouth twice a day, which are difficult for children to swallow. Therefore, there was a need to study a tacrolimus formulation that was easier to use in children. Modigraf® is a medicine that contains tacrolimus granules that can be mixed with water. Modigraf was made to be easier to swallow by children.

This study was conducted in children who had received a single organ transplant. The purpose of this study was to offer continued treatment with Modigraf to patients who were in the F506-CL-0403 study until these patients were able to take the capsule form of tacrolimus (Prograf). The study was an extension of study F506-CL-0403 and had 2 parts:

- Part A of the study answered the question how effective Modigraf was in helping transplanted organs survive at least 3 months.
- Part B of the study looked at the changes in the doses of each study medicine and how much tacrolimus was in the blood after patients stopped taking Modigraf and started taking Prograf. It was also important to find out what unwanted effects these patients had when transitioning from Modigraf to Prograf.

Part A of the study took place at 11 clinics in the United Kingdom, Spain, Germany, Belgium, Poland and France. Part B of the study took place at 4 clinics in the United Kingdom, Spain and Germany. The study started in June 2011 and ended in April 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. What this means is that all patients knew that they took Modigraf and Prograf.

Children enrolled in F506-CL-0403 study could take part in this study if:

- They were 12 years old or younger when they started the F506-CL-403 study
- They had received at least 1 dose of Modigraf in the F506-CL-0403 study

During part A of the study, the study doctor did a check-up of the patients at each study visit. At visit 1 (day 1), patients were checked to see if they could be in part A of the study. Patients who could be in the study took the first dose of Modigraf at visit 1 (day 1). The first dose of Modigraf was the same as the final dose taken in the F506-CL-0403 study. Modigraf was taken by mouth 2 times per day. Thereafter, the study doctor adjusted the dose of Modigraf based on the specific needs of the patient. Blood samples were collected at each visit during the study to check the amount of tacrolimus in the blood. Patients were able to continue treatment in part A of this study for a maximum of 1 year but not less than 3 months. There was no time limit on when patients could enter part B. Once the study doctor had determined that a patient could begin to take the Prograf capsule, that patient could continue treatment in part B of this study.

During part B of the study, patients were checked to see if they could be in part B of the study at visit 1 (day 1). Patients who could be in the study took their prescribed dose of Modigraf at visit 1 (day 1). On day 2, patients stopped taking Modigraf and began taking their first dose of Prograf. The dose of Prograf was similar to the dose of Modigraf. Thereafter, the study doctor adjusted the dose of Prograf based on the specific needs of the patient. Blood samples were collected at least 4 times (between days 3 and 16) to check the amount of tacrolimus in the blood. Patients took Prograf that was supplied for this study for 1 month. Thereafter, patients took Prograf that was supplied by their pharmacy.

Forty-seven (47) patients were in part A of the study and took at least 1 dose of Modigraf. Six (6) patients were in part B of the study and took at least 1 dose of Modigraf and Prograf.

	Number of Patients	
	Part A (out of 47 patients)	**Part B (out of 6 patients)**
Age at enrollment into previous study (F506-CL-0403)		
Aged less than 4 years	33	0
Aged more than 4 years to 12 years	14	5
Aged 13 years	0	1
Sex		
Male	32	4
Female	15	2
Clinic location		
European Union		
Belgium	3	0
France	3	0
Germany	5	3
Poland	1	0
Spain	26	1
United Kingdom	9	2

What Were the Study Results?

Part A of the study answered the question how effective Modigraf was in helping transplanted organs survive at least 3 months. Nine (9) patients had symptoms of transplant rejection by the body before 3 months of treatment.

Part B of the study looked at the changes in the doses of each study medicine and how much tacrolimus was in the blood after patients stopped taking Modigraf and started taking Prograf. During part B of the study, 5 of the 6 patients had their dose of Prograf adjusted at least once during the study.

The table below shows how much tacrolimus was in the blood of patients on the last day they took Modigraf and after they started to take Prograf.

	Amount of Study Medicine in Blood (ng/mL is the unit that measures the amount of the medicine in blood)	
Type of Transplant	**Modigraf**	**Prograf**
Patients with kidney transplant	4.3 to 7.1 ng/mL	5.2 to 5.6 ng/mL
Patients with liver transplant	3.1 ng/mL	2.8 to 9.0 ng/mL
Patients with heart transplant	Not available	6.3 ng/mL

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.

Thirty-two (32) patients who took at least 1 dose of Modigraf during part A had 1 or more adverse reactions. One (1) patient experienced adverse reactions during part B of the study. The table below shows the most common adverse reactions experienced by these patients.

Adverse Reaction	**Part A Number of Patients (out of 47 patients)**	**Part B Number of Patients (out of 6 patients)**
Any adverse reaction	32	1
Decreased blood level of magnesium	8	0
More acid than normal in blood	6	0
High blood pressure	7	0
Diarrhea	4	0
Vomiting	4	0
Loss of kidney function	4	0
Epstein-Barr virus infection	2	0
Infection affecting the lower respiratory tract (lungs, bronchi and trachea)	2	0
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	2	1
Lack of enough red blood cells (anemia)	2	0
Fever	2	0
Cough	2	1
Cold	0	2

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

Twelve (12) patients experienced serious adverse reactions in part A. No patients experienced serious adverse reactions in part B. Infection of the vocal chords and lungs (experienced by 2 patients) was the most common serious adverse reaction. The table below shows the serious adverse reactions in part A.

Serious Adverse Reaction	**Part A Number of Patients (out of 47 patients)**
Any serious adverse reaction	12
Infection affecting the lower respiratory tract (lungs, bronchi and trachea)	2
Severe illness in which the bloodstream is overwhelmed by bacteria	1
Infection caused by the cytomegalovirus (CMV)	1
Inflammation (swelling and redness) of the stomach lining	1
Bacterial infection of the small intestines	1

Serious Adverse Reaction	Part A Number of Patients (out of 47 patients)
Protozoan infection of the gastrointestinal tract	1
Urinary tract infection	1
Urinary tract infection caused by bacteria	1
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	1
Body temperature increased	1
Increased blood level of liver enzymes	1
Increased blood level of liver enzymes (ALT/SGPT and AST/SGOT)	1
Situation where a substance affects the activity of another drug when administered together (drug interaction)	1
Fever	1
More acid than normal in the blood	1
Excessive loss of body water	1
Production of small amounts of urine	1
Abnormal function of kidneys	1
Abnormal enlargement or thickening of the heart muscle	1
Fast heartbeat usually originating in an area located above the ventricles	1
Tendency of some treatments to cause damage to the nervous system (neurotoxicity)	1
Abnormal buildup of fluid in the lungs	1
Failure to take study medicine	1

Where Can I Learn More About This Study?

This document reflects the information available as of March 2018. This summary of the clinical study results is available online at http://www.astellasclinicalstudy results.com.

Astellas may perform additional studies to better understand tacrolimus granules.

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 granules, please discuss these with your doctor.

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