Summary of Results for Laypersons

What was the Study Called?

A Multicentre, Open-label, Pharmacokinetic Study of Modigraf® (Tacrolimus Granules) in *de Novo* Paediatric Allograft Recipients. This is also known as the OPTION 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. There are medicines that reduce the strength of the immune system. These medicines help prevent the body from rejecting the transplanted organ. As a result, the transplanted organ will survive longer.

There are several medicines that help prevent the body from rejecting a transplanted organ. These medicines include tacrolimus. Tacrolimus comes in capsules, which are difficult for children to swallow. Modigraf is tacrolimus granules that can be mixed with water. Modigraf was made to be easier to swallow by children.

This study tested Modigraf in children who received an organ transplant for the first time. The main question this study helped answer was how well the study medicine is absorbed into the body and how long it stays in the body. It was also important to find out what unwanted effects these patients had from the study medicine.

This study took place at 10 clinics in Belgium, France, Germany, Poland, Spain and the UK. The study took place from June 2011 to February 2015. 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, which means that all patients knew that they took Modigraf.

Patients could take part in the study if:

- They were 12 years old or younger.
- They had received a liver, kidney or heart transplant.

Patients could not take part in the study if:

- They had received another organ transplant in the past.
- They had received an organ from a donor with a different blood type than their own.
- 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.

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.

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

- They had a high immunological risk; they had a more than 50% human antibody score on a blood test against a type of white blood cells in their donor pool in the past 6 months. This score means that their body would reject a kidney transplant from their donor pool more than 5 out of 10 times. About 100 blood donors in their area were in their donor pool.
- Their donor kidney was kept chilled for more than 30 hours before it could be transplanted.

During this 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. Patients could be in the study if they took the study medicine within 24 hours after the start of blood flow to their donor organ. Patients who received a heart transplant could take the study medicine within 5 days after the start of blood flow to their donor organ. All patients took 2 doses of study medicine by mouth per day. The total daily dose was 0.3 mg per kg body weight at first. Thereafter, the study doctor adjusted the dose based on the specific needs of the patient.

Visits 2, 3 and 4 were 1, 7 and 14 days after the start of study treatment, respectively. At these visits, the study doctor did a safety check-up. At visit 2, the study doctor took 7 blood samples. One sample was taken before the morning dose of study medicine. The remaining 6 samples were taken between 0.5 and 12 hours after the morning dose. At visit 3 or after patients had the same dose for at least 4 days, the study doctor again took those 7 blood samples.

A total of 52 patients were in this study and received at least 1 dose of study medicine.

	Number of Patients (out of 52 patients)
Age Group	
Aged 28 days to 23 months	17
Aged 2 to 11 years	34
Aged 12 years	1
Sex	
Girls	17
Boys	35
Clinic Location	
EU Countries	52
Belgium	3
France	3
Germany	7
Poland	1
Spain	26
The UK	12
Outside EU	0

What Were the Study Results?

This study tested Modigraf in children who received a solid organ transplant for the first time. The transplanted organ was liver, kidney or heart. The level of study medicine in the blood of these children was comparable to that in adults with a solid organ 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.

The table below shows the most common adverse reactions experienced by patients who received at least 1 dose of study medicine. More patients in the liver transplant group than in the other transplant groups had high blood pressure. More patients in the liver transplant group than in the other transplant groups had a toxic blood level of tacrolimus.

Adverse Reaction	Heart Transplant (out of 17 patients)	Liver Transplant (out of 20 patients)	Kidney Transplant (out of 15 patients)
High blood pressure	1 (5.9%)	9 (45.0%)	0
A toxic blood level of tacrolimus	0	5 (25.0%)	1 (6.7%)
Kidneys not working well	2 (11.8%)	2 (10.0%)	0
Diarrhea	1 (5.9%)	0	2 (13.3%)
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	1 (5.9%)	0	2 (13.3%)
Damage to the kidneys	2 (11.8%)	0	0

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care. Eight patients experienced serious adverse reactions. The table below shows these serious adverse reactions.

Serious Adverse Reaction	Heart Transplant (out of 17 patients)	Liver Transplant (out of 20 patients)	Kidney Transplant (out of 15 patients)
A toxic blood level of tacrolimus	0	3 (15.0%)	0
Pneumonia	0	0	1 (6.7%)
Severe illness in which the bloodstream is overwhelmed by bacteria	0	1 (5.0%)	0
Kidney failure	0	1 (5.0%)	0
Kidneys not working well	1 (5.9%)	0	0
Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)	0	0	1 (6.7%)

None of the patients died during the study.

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.

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