Summary of Results for Laypersons

What was the Study Called?

A Multicenter, Randomized, Comparison, Open-label, Phase IV Study to Assess the Efficacy and Safety of Advagraf® Switching From Cyclosporine Between the Group That Was Treated With a 50% Reduced Corticosteroid and the Group With Maintained Corticosteroid for Stable Kidney Transplant Recipients. This is also known as the COSMOS study.

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. A combination of corticosteroids and another medicine is usually used to reduce the strength of the immune system in patients with a transplant. The other medicine could be cyclosporine (also known as Amadra, Cicporal, Ciclosporin FC, Ciclosporin Mylan, Ciclosporin BMD, Ciclosporin Nichi-iko, Ciclosporin Towa, Neoral, Sandimmune, Restasis and Gengraf) or Advagraf (also known as Graceptor, tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL, FK506E, MR4 or tacrolimus modified-release). The medicine combination prevents the body from rejecting organ transplants. Patients who take Advagraf in combination with the usual (high) dose of corticosteroids are at risk for developing diabetes.

There was a need for studying new treatment options. Advagraf plus half the usual dose of corticosteroids was tested to see if this combination could reduce unwanted effects.

This study was conducted in patients who had received a kidney transplant. They took cyclosporine and corticosteroids to prevent their body from rejecting their kidney transplant. At study start, the patients switched to Advagraf and corticosteroids. Half of the patients continued to take the same dose of corticosteroids for 24 weeks. The other half slowly lowered their corticosteroid dose from weeks 4 to 12 until it was half of their starting dose. They continued to take this dose from weeks 12 to 24.

The main question this study helped answer was did the kidney work differently after a 24-week treatment with Advagraf and corticosteroids. To assess kidney function, the study looked at the change in estimated glomerular filtration rate or eGFR for short.

It was also important to find out what unwanted effects these patients had from the study medicines.

This study took place at 19 clinics in South Korea. The study took place from November 2013 to November 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. This means that all patients knew that they took Advagraf in combination with corticosteroids.

Patients could take part in the study if:

- They were at least 20 years.
- They had received a kidney transplant at least 12 months before study start.
- They took cyclosporine and corticosteroids for at least 4 weeks before study start.
- Their combination treatment of cyclosporin and corticosteroids was unchanged for at least 4 weeks before study start.
- Their eGFR was at least 30 mL/min.

Patients could not take part in the study if:

- They had received a transplant of an organ that was not a kidney.
- Within 12 weeks before study start, they had symptoms that showed their body was rejecting their transplant. Or within 24 weeks before study start, they had needed treatment for such symptoms.
- They developed cancer after their transplantation. This did not include skin cancer that was cured.
- They had received an organ from a donor with the exact same immune system markers.
- The kidney disease that led them to require a kidney transplant had a high chance of recurring in the transplanted kidney.
- They had increased blood levels of a liver enzyme (alanine aminotransferase/serum glutamic pyruvic transaminase or aspartate aminotransferase/serum glutamic oxaloacetic transaminase) at least 2 times the normal level. Increased blood levels of these liver enzymes indicate that liver cells are damaged.

During this study, the study doctor did a check-up of the patients at 6 study visits. At visit 1, patients were checked to see if they could be in the study. At visit 2, patients who could be in the study were picked for 1 of the 2 following daily treatments by chance alone:

- Advagraf and continue same dose of corticosteroids: Patients took the combination of Advagraf (0.05 to 0.07 mg per kg of body weight each day) and corticosteroids (dose taken at study start) for 24 weeks.
- Advagraf and half of previous dose of corticosteroids: Patients took Advagraf (0.05 to 0.07 mg per kg of body weight each day) for 24 weeks. They took corticosteroids (starting dose) for 3 weeks. From weeks 4 to 12, the corticosteroid dose was slowly lowered until it was half of the starting dose. From weeks 12 to 24, the patients continued to take half of the starting dose of corticosteroids.

Visits 3, 4, 5 and 6 were 1, 4, 12 and 24 weeks after the start of study treatment, respectively. At these visits, the study doctor did a safety check-up. The study doctor also took a blood sample in the morning before the dose of Advagraf.

A total of 150 patients were in this study. A total of 149 patients received at least 1 dose of study medicine.

- A total of 77 patients took Advagraf and starting dose of corticosteroids for 24 weeks.
- A total of 72 patients took Advagraf for 24 weeks and half of the starting dose of corticosteroids from weeks 12 to 24.

	Number of Patients (out of 149 patients)
Age Group	
Aged 30 to 39 years	19
Aged 40 to 49 years	41
Aged 50 to 59 years	51
Aged 60 years or older	38
Sex	
Women	56
Men	93
Clinic Location	
EU Countries	0
Outside EU	149
South Korea	149

What Were the Study Results?

The patients in this study had received a kidney transplant. All patients took Advagraf for 24 weeks. About half of the patients took the same dose of corticosteroids for 24 weeks. The other patients slowly lowered their corticosteroid dose from weeks 4 to 12 until it was half of their starting dose. They continued to take half of their starting dose from weeks 12 to 24. The study looked at the change in eGFR after the 24-week treatment with Advagraf and corticosteroids. The average eGFR increase was 3.39 mL/min/1.73 m^2 in patients who took Advagraf and the starting dose of corticosteroids. The average eGFR increase was 1.53 mL/min/1.73 m^2 in patients who took Advagraf and half of the starting dose of corticosteroids. A test showed that the difference between the treatments was likely due to chance.

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 reaction experienced by patients who received at least 1 dose of study medicine.

Adverse Reaction	Advagraf and Half of Starting Dose of Corticosteroids (out of 72 patients)	Advagraf and Starting Dose of Corticosteroids (out of 77 patients)
Diarrhea	4 (5.6%)	4 (5.2%)

An adverse reaction is considered "serious" when it is life-threatening, causes lasting problems or needs hospital care. Two patients (1 in each treatment group) experienced

serious adverse reactions. The serious adverse reactions were increased blood sugar level and headache or head pain.

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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