

Plain Language Summary of Study Results

Astellas is grateful to the patients who took part in this clinical study. Thank you.

What was the Study Called?

Astagraf XL® to Understand the Impact of Immunosuppression on De Novo DSA Development and Chronic Immune Activation in Kidney Transplantation.

This is also known as the ASTOUND study.

Why was this Study Needed?

The immune system is part of the body that fights foreign objects or infections. After organ transplant surgery, the immune system recognizes the new organ as a foreign object and will try to reject it. One of the ways it does this is by making antibodies to the new organ. These are also known as donor specific antibodies (DSA).

Tacrolimus is a type of medicine called an immunosuppressant, which controls the response of the immune system. This helps to stop the body rejecting organ transplants. For kidney transplants, the number of antibodies and other immune responses to the new kidney increase over time. In due course, this can cause damage to the transplanted kidney which might lead to kidney failure. Some think these problems might get worse if the amount of tacrolimus medicine in the body goes up and down too often. One way this could happen is if patients don't take this medicine regularly over time. Another way is how the medicine acts in the body.

Tacrolimus is taken by mouth, twice daily. Another form of tacrolimus is Astagraf XL (also known as tacrolimus extended-release), also taken by mouth. Astagraf XL is taken once daily which might help patients remember to take it regularly. Also it might go up and down in the body less often than the form of tacrolimus taken twice daily.

In this study, patients who had kidney transplants either took Astagraf XL capsules once daily or tacrolimus capsules twice daily. They did this after their kidney transplant for 12 months. The researchers wanted to know how many patients had antibodies and other immune responses to their new kidney over time. They also wanted to know if the number of patients who had these responses was different between those who took Astagraf XL once daily and those who took tacrolimus twice daily.

Also it was important to learn if these patients had any medical problems from the study medicines.

The study started in September 2016 and ended in June 2019. The sponsor of this study (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 each patient and the study doctors knew which form of tacrolimus that patient took (Astagraf XL once daily or tacrolimus twice daily).

This study included boys, men, girls and women between 16 and 70 years old. These patients had received a kidney transplant.

What happened during the Study?

During the study, the study doctor did a check-up of the patients at several study visits. At the first visit, patients were checked to see if they could take part in the study. Patients who could take part were picked for 1 of 2 treatments by chance alone.

Patients took 1 of 2 of the following forms of tacrolimus:

- Astagraf XL once daily: Patients took Astagraf XL capsules once a day. They started on a dose of 0.15 milligrams for every kilogram of body weight. This is also known as 0.15 mg/kg. Then the study doctor decided the dose for each patient.
- Tacrolimus twice daily: Patients took tacrolimus capsules twice a day. The study doctor decided the dose for each patient.

Patients took either Astagraf XL once daily or tacrolimus twice daily for 12 months.

This study took place at 30 clinics in the US. 599 patients were in the study. Out of these patients, 575 patients took at least 1 dose of study medicine.

	Number of Patients
Age Group	
Aged less than 17 years	0
Aged 18 to 34 years	85
Aged 35 to 49 years	182
Aged 50 to 70 years	308
Aged 70 years or older	0
Sex	
Men or boys	383
Women or girls	192

What Were the Study Results?

A total of 288 patients took Astagraf XL once daily and 287 patients took tacrolimus twice daily.

How many patients had an overall immune response within 12 months of receiving their new kidney?

After 12 months, antibodies and other immune responses were measured together (combined) to record the overall immune response.

- Astagraf XL once daily: 98 patients (35.6%, or 98 out of 275 patients) showed an overall immune response
- Tacrolimus twice daily: 96 patients (34.4%, or 96 out of 279 patients) showed an overall immune response

Statistical tests showed there was no real difference in the overall immune response between patients who took Astagraf XL once daily and those who took tacrolimus twice daily.

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.

In this study, adverse reactions were reported in 2 ways; those **possibly** caused by a medicine or treatment and **probably** caused by a medicine or treatment.

The following patients experienced adverse reactions in this study:

Possible adverse reactions:

- Astagraf XL once daily: 197 patients (68.4%, or 197 out of 288 patients)
- Tacrolimus twice daily: 180 patients (62.7%, or 180 out of 287 patients)

Probable adverse reactions:

- Astagraf XL once daily: 109 patients (37.8%, or 109 out of 288 patients)
- Tacrolimus twice daily: 85 patients (29.6%, or 85 out of 287 patients)

The table below shows the most common adverse reactions experienced by patients who took at least 1 dose of study medicine in this study. The table also shows other important adverse reactions which directly affected the transplanted kidney.

Adverse Reaction	Astagraf XL once daily (out of 288 patients)	Tacrolimus twice daily (out of 287 patients)
Common Adverse Reactions		
Uncontrolled trembling or shaking movements in one or more parts of your body (probable adverse reaction)	58 (20.1%)	47 (16.4%)
Decreased blood level of magnesium (possible adverse reaction)	34 (11.8%)	27 (9.4%)
Diarrhea (possible adverse reaction)	30 (10.4%)	35 (12.2%)
Uncontrolled trembling or shaking movements in one or more parts of your body (possible adverse reaction)	30 (10.4%)	33 (11.5%)
Infection with the BK virus (a common virus) (possible adverse reaction)	29 (10.1%)	21 (7.3%)
Increased blood level of potassium (possible adverse reaction)	26 (9.0%)	29 (10.1%)
Other Important Adverse Reactions		
Kidney transplant rejection (patient's body attacked the new kidney) (possible adverse reaction)	5 (1.7%)	10 (3.5%)
Kidney transplant rejection (patient's body attacked the new kidney) (probable adverse reaction)	4 (1.4%)	3 (1.0%)

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

The total number of patients who had serious adverse reactions are shown below.

Possible serious adverse reactions:

- Astagraf XL once daily: 66 patients (22.9%, or 66 out of 288 patients)
- Tacrolimus twice daily: 58 patients (20.2%, or 58 out of 287 patients)

Probable serious adverse reactions:

- Astagraf XL once daily: 22 patients (7.6%, or 22 out of 288 patients)
- Tacrolimus twice daily: 17 patients (5.9%, or 17 out of 287 patients)

The table below shows the most common serious adverse reactions experienced by patients that were **possibly** caused by the study medicines (possible serious adverse reaction)

Possible Serious Adverse Reaction	Astagraf XL once daily (out of 288 patients)	Tacrolimus twice daily (out of 287 patients)
Sudden decrease of kidney function	8 (2.8%)	13 (4.5%)
Urinary tract infection	8 (2.8%)	4 (1.4%)
Kidney transplant rejection (patient's body attacked the new kidney)	4 (1.4%)	7 (2.4%)

There were no common serious adverse reactions that were **probably** caused by the study medicines (**probable** serious adverse reaction).

4 patients died during the study (2 took Astagraf XL once daily and 2 took tacrolimus twice daily). One death could have been caused by tacrolimus twice daily. None of the other deaths were caused by the study medicines (Astagraf XL once daily or tacrolimus twice daily). Also, 1 patient who took tacrolimus twice daily died just after the study ended. This was not caused by the study medicine (tacrolimus twice daily).

Where Can I Learn More About This Study?

This document is a short summary of the main results from this study. You can find this summary and more information about this study 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. This summary only shows the results of this 1 study. Your doctor may help you understand more about the results of this study.

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