Study Number: PMR-EC-1213
Study Name: ADDRESS
EudraCT number: NA
EU PAS register number: not registered
ClinicalTrials.gov Identifier: NCT02057484

Summary of Results for Laypersons

What was the Study Called?

A long-term follow-up of adult kidney and liver allograft recipients previously enrolled into a tacrolimus (Advagraf) trial. A multicenter non-interventional post authorization study (PAS). This was also known as the ADDRESS 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. Advagraf (also known as Graceptor, tacrolimus prolonged-release, tacrolimus extended-release, Astagraf XL, FK506E, MR4 or tacrolimus modified-release) is a prescription medicine that reduces the strength of the immune system ("immunosuppressant"). It prevents the body from rejecting organ transplants. The standard treatment for patients with organ transplants is to take immunosuppressants every day as prescribed by their doctors. Approximately half of patients with transplants who are taking immunosuppressants lose their transplants after 10 years. Clinical studies showed that Advagraf works well in the short term (up to 1 year). But there is not yet enough information about how Advagraf works over the long term. Therefore, there was a need to record the survival of kidney and liver transplants in patients treated with Advagraf over the 5 years after their transplant surgery.

This study was conducted in patients who had a kidney or liver transplant. After their transplant surgery, patients had taken Advagraf in an earlier study. The main question this study helped answer was what was the overall survival rate of the kidney and liver transplants in the long term. That is the proportion of patients who still had their transplants 5 years after their transplant surgery. During the study, the study doctor also asked patients what unwanted effects they had from their standard immunosuppressant medicines.

Data collection for this study started in March 2014 and ended in October 2017. When the study ended, 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 a "noninterventional" study. This means that the study doctor did not give study medicine to the patients. During the study, patients continued taking their standard immunosuppressant medicines (Advagraf, other tacrolimus formulations or other immunosuppressants) as prescribed by their doctors. Those standard immunosuppressant medicines were not considered study medicines.

This was also a follow-up study. This means that the patients in this study had taken part in an earlier study of Advagraf.

Clinical studies have a list of requirements for patients who can be in a study ("inclusion" criteria) and patients who cannot take part in a study ("exclusion" criteria). The requirements for this study are listed below.

Patients aged 18 years or more could be in the study if:

- They had taken part in an earlier Advagraf study:
  - PMR-EC-1106 (also known as the DIAMOND study)
  - PMR-EC-1211 (also known as the ADVANCE study)
  - PMR-EC-1212 (also known as the ADHERE study)

During the study, the study doctor did a check-up of the patients at several study visits. At visit 1, patients were checked to see if they could be in the study. The patients could remain in the study for up to 5 years after their transplant surgery.

This study took place at a total of 140 clinics in

- 20 countries of the European Union (at the time of the study: Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Spain, Sweden and United Kingdom)
- 5 countries outside of the European Union (Belarus, Canada, Russia, South Korea and Switzerland)

2819 patients took at least 1 dose of Advagraf in 1 of 3 earlier Advagraf studies (DIAMOND, ADVANCE or ADHERE). For 2018 out of the 2819 patients, information was collected during this study.

	Number of Patients		
	DIAMOND (out of 617 patients)	**ADVANCE (out of 814 patients)**	**ADHERE (out of 587 patients)**
Age Group			
Aged younger than 50 years	156	357	258
Aged 50 to 65 years	403	357	256
Aged 66 to 75 years	58	95	71
Aged older than 75 years	0	5	2
Sex			
Men	443	530	384
Women	174	284	203

What Were the Study Results?

This study in patients with a kidney or liver transplant looked at the proportion of patients who still had their transplants 5 years after their transplant surgery.

The estimated proportion of patients who still had their transplants 5 years after their transplant surgery was

- Approximately 74 out of every 100 patients (73.5%) who had taken part in the DIAMOND study

- Approximately 88 out of every 100 patients (88.1%) who had taken part in the ADVANCE study
- 84 out of every 100 patients (84.0%) who had taken part in the ADHERE study

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" in this study is any medical problem or "adverse event" that is judged by the study doctor to be possibly caused by Advagraf or other tacrolimus formulations that patients were taking during the study as their standard immunosuppressant medicines.

The table below shows the most common adverse reactions.

Adverse Reaction	**DIAMOND (out of 617 patients)**	**ADVANCE (out of 814 patients)**	**ADHERE (out of 587 patients)**
Any adverse reaction	18 (2.9%)	50 (6.1%)	50 (8.5%)
Urinary tract infection	1 (0.2%)	3 (0.4%)	4 (0.7%)
Cancer that begins in cells that form the epidermis (outer layer of the skin)	0	0	5 (0.9%)
Cancer that begins in the lower part of the epidermis (the outer layer of the skin)	0	1 (0.1%)	5 (0.9%)
Common cold	0	0	5 (0.9%)
Diarrhea	0	4 (0.5%)	1 (0.2%)
Flu	0	1 (0.1%)	4 (0.7%)
Kidneys not working well	0	1 (0.1%)	3 (0.5%)
Lung infection	0	4 (0.5%)	2 (0.3%)
Shingles (herpes zoster)	0	1 (0.1%)	3 (0.5%)
Uncontrolled trembling or shaking movements in one or more parts of your body	0	1 (0.1%)	4 (0.7%)
Urinary tract infection caused by *Escherichia coli* bacteria	0	4 (0.5%)	4 (0.7%)

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

68 patients experienced serious adverse reactions. The table below shows the serious adverse reactions experienced by at least 2 patients.

Serious Adverse Reaction	DIAMOND (out of 617 patients)	ADVANCE (out of 814 patients)	ADHERE (out of 587 patients)
Any serious adverse reaction	14 (2.3%)	28 (3.4%)	26 (4.4%)
Disease that causes inflammation and sores, called ulcers, in the lining of the rectum and colon	2 (0.3%)	0	0
Kidney failure	2 (0.3%)	0	0
Cancer of the head and neck that begins in squamous cells (thin, flat cells that form the surface of the skin, eyes and various internal organs and the lining of hollow organs and ducts of some glands)	1 (0.2%)	1 (0.1%)	1 (0.2%)
Cancer that begins in squamous cells (thin, flat cells that form the surface of the skin, eyes and various internal organs and the lining of hollow organs and ducts of some glands)	1 (0.2%)	0	2 (0.3%)
Cancer that begins in cells that form the epidermis (the outer layer of the skin)	0	0	3 (0.5%)
Cancer that begins in glandular (secretory) cells of the colon	0	2 (0.2%)	0
Cancer that begins in the lower part of the epidermis (the outer layer of the skin)	0	1 (0.1%)	4 (0.7%)
Diarrhea	0	2 (0.2%)	1 (0.2%)
Flu	0	1 (0.1%)	2 (0.3%)
Kidney infection	0	2 (0.2%)	1 (0.2%)
Kidneys not working well	0	0	3 (0.5%)
Lung infection	0	3 (0.4%)	2 (0.3%)
Lung infection that starts in the small airways of the lung	0	0	2 (0.3%)
Severe illness in which the bloodstream is overwhelmed by bacteria	0	2 (0.2%)	0
Severe illness in which the bloodstream is overwhelmed by bacteria that started as an infection in the urinary tract	0	1 (0.1%)	2 (0.3%)
Sudden kidney failure	0	1 (0.1%)	1 (0.2%)
Urinary tract infection caused by *Escherichia coli* bacteria	0	3 (0.4%)	1 (0.2%)

A total of 25 patients died during the study: 4 patients who had taken part in the DIAMOND study; 7 patients who had taken part in the ADVANCE study; and 14 patients who had taken part in the ADHERE study. The deaths of 3 patients who had taken part in the ADHERE study could have been related to Advagraf or other tacrolimus formulations that patients were taking as their standard immunosuppressant medicines. The table below shows the 4 adverse reactions that led to those 3 deaths.

Adverse Reaction Leading to Death	DIAMOND (out of 617 patients)	ADVANCE (out of 814 patients)	ADHERE (out of 587 patients)
Any adverse reaction leading to death	0	0	3 (0.5%)
Cancer that begins in the glands that line the inside of an organ	0	0	1 (0.2%)
Cancer of the head and neck that begins in squamous cells (thin, flat cells that form the surface of the skin, eyes and various internal organs and the lining of hollow organs and ducts of some glands)	0	0	1 (0.2%)
Cancer that has come back in tissues of the small intestine (the part of the digestive tract between the stomach and the large intestine)	0	0	1 (0.2%)
The spread of cancer cells from the place where they first formed to another part of the body	0	0	1 (0.2%)

Where Can I Learn More About This Study?

This document is a short summary of the main results from this study and reflects the information available as of September 2018. 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. If you have questions about Advagraf, please discuss these with your doctor.

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