Summary of Results for Laypersons

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

What was the Study Called?

A Long-Term Follow up Study to Evaluate the Safety and Efficacy in Transplant Recipients Treated with Modified Release Tacrolimus, FK506E (MR4), Based Immunosuppression Regimen

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). At the start of this study, there was not yet enough information about how Advagraf works over the long term. Therefore, there was a need to study the survival of organ transplants and the survival of patients after Advagraf treatment for up to 5 years.

This study was conducted in patients who had a kidney, liver or heart transplant. After their transplant surgery, patients had taken Advagraf in a previous study. This study was a long-term continuation of those previous studies. Patients started out taking the same dose of Advagraf that they took in the previous study. This study helped answer 2 main questions. One of the main questions was what was the overall survival rate of the organ transplants in the long term. That is the proportion of patients who still had working transplants after taking Advagraf for up to 5 years. The other main question was what was the overall survival rate of the patients in the long term. That is the proportion of patients who were still alive after taking Advagraf for up to 5 years. It was also important to find out what unwanted effects these patients had from the study medicine.

The study started in February 2003 and ended in October 2009. 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 an "open-label" study. This means that all patients and the study doctors knew which study medicine the patients took (Advagraf).

This study included adult women and men who had an organ transplant. They took at least 1 dose of Advagraf in 1 of 10 previous studies. In Studies 1, 2, 5, 6, 7, patients took only

Advagraf. In Studies 3, 4, 8 and 9, patients took Prograf for the first few days and thereafter took Advagraf. In Study 10, patients took cyclosporine A for at least 12 months and thereafter took Advagraf. Advagraf, Prograf and Cyclosporine A are all medicines that reduce the strength of the immune system. Prograf and Advagraf are different forms of tacrolimus. The difference is that Prograf capsules are to be taken twice a day and Advagraf capsules once a day.

- FG-506-11-01 (referred to as Study 1)
- FG-506E-12-01 (referred to as Study 2)
- FG-506E-12-02 (referred to as Study 3)
- FG-506-15-02 (referred to as Study 4)
- FG-506E-11-03 (referred to as Study 5)
- FG-506E-12-03 (referred to as Study 6)
- PMR-EC-1210 (referred to as Study 7)
- PMR-EC-1105 (referred to as Study 8)
- PMR-EC-1205 (referred to as Study 9)
- PMR-EC-1209 (referred to as Study 10)

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 be in the study. Patients who could be in the study took their dose of Advagraf once a day for up to 6 years. Their starting dose was the same dose that they took in the previous Advagraf study. They also took their prescribed immunosuppressant medicines, if any.

This study took place at a total of 128 clinics in

- 15 countries of the European Union (at the time of the study: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Spain, Sweden and United Kingdom)
- 9 countries outside of the European Union (Australia, Brazil, Canada, Mexico, New Zealand, Russia, South Africa, Switzerland and USA)

850 patients were in the study and took at least 1 dose of study medicine.

	Number of Patients									
Previous Advagraf Study in Which Patients Had Taken Part	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Total Number of Patients in Previous Advagraf Study	47	47	67	79	130	191	9	85	107	88
Age Group										
Aged between 20 and 29 years	2	8	8	4	1	19		3	4	1
Aged between 30 and 39 years	6	6	15	10	10	31	*Age*	7	21	10
Aged between 40 and 49 years	17	16	18	17	24	52	*not*	16	26	18
Aged between 50 and 59 years	15	13	17	23	61	59	*known*	33	30	30
Aged 60 years or older	7	4	9	25	34	30		26	26	29
Sex										
Men	36	27	48	64	91	117	5	61	80	52
Women	11	20	19	15	39	74	4	24	27	36

What Were the Study Results?

This study looked at the proportion of patients who still had working transplants after taking Advagraf for up to 5 years. That is the number of treated patients with still working transplants compared to the total number of treated patients. The study also looked at the proportion of patients who were still alive after taking Advagraf for up to 5 years. That is the number of treated patients who were still alive compared to the total number of treated patients.

Study results for patients from previous Studies 1, 2, 3 and 4:

The table below shows the study results for patients from previous studies 1, 2, 3 and 4 after they took Advagraf for 5 years.

Study Results After Advagraf Treatment for 5 Years	Study 1 (out of 47 patients)	Study 2 (out of 47 patients)	Study 3 (out of 67 patients)	Study 4 (out of 79 patients)
Estimated proportion of patients who still had working transplants	90.9%	100%	92.2%	90.3%
Estimated proportion of patients who were still alive	90.9%	100%	93.6%	90.3%

Study results for patients from previous Studies 5 and 6:

The table below shows the study results for patients from previous studies 5 and 6 after they took Advagraf for 2 years.

Study Results After Advagraf Treatment for 2 Years	Study 5 (out of 130 patients)	Study 6 (out of 191 patients)
Estimated proportion of patients who still had working transplants	95.4%	97.4%
Estimated proportion of patients who were still alive	95.4%	99.3%

Study results for patients from previous Study 7:

During this study, all 9 patients (100%) from previous Study 7 had working transplants and stayed alive.

Study results for patients from previous Studies 8, 9 and 10:

The table below shows the study results for patients from previous studies 8, 9 and 10 after they took Advagraf for 1 year.

Study Results After Advagraf Treatment for 1 Year	Study 8 (out of 85 patients)	Study 9 (out of 107 patients)	Study 10 (out of 88 patients)
Estimated proportion of patients who still had working transplants	100%	99.0%	100%
Estimated proportion of patients who were still alive	100%	100%	100%

The study results showed that Advagraf worked well over the long-term.

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 (in **bolded** font) experienced by patients from previous Studies 1 through 5 who took at least 1 dose of Advagraf in this study. There were no most common adverse reactions in Studies 6 through 10.

Previous Advagraf Study in Which Patients Had Taken Part	**Study 1 (out of 47 patients)**	**Study 2 (out of 47 patients)**	**Study 3 (out of 67 patients)**	**Study 4 (out of 79 patients)**	**Study 5 (out of 130 patients)**
Adverse Reaction					
Any adverse reaction	47 (100%)	42 (89.4%)	44 (65.7%)	56 (70.9%)	112 (86.2%)
High blood pressure	**14 (29.8%)**	**6 (12.8%)**	3 (4.5%)	**8 (10.1%)**	**33 (25.4%)**
Kidney failure	**11 (23.4%)**	0	0	5 (6.3%)	**24 (18.5%)**
A disease in which the body does not use insulin properly (type 2 diabetes)	**11 (23.4%)**	2 (4.3%)	1 (1.5%)	3 (3.8%)	12 (9.2%)
Uncontrolled trembling or shaking movements in one or more parts of your body	**11 (23.4%)**	**12 (25.5%)**	1 (1.5%)	1 (1.3%)	8 (6.2%)
Headache or head pain	**10 (21.3%)**	2 (4.3%)	0	5 (6.3%)	9 (6.9%)
Increased blood sugar level	**10 (21.3%)**	**5 (10.6%)**	0	2 (2.5%)	4 (3.1%)
Liver infection caused by the hepatitis C virus	**7 (14.9%)**	0	0	0	**13 (10.0%)**
Diarrhea	**6 (12.8%)**	3 (6.4%)	2 (3.0%)	3 (3.8%)	2 (1.5%)
Common cold	**5 (10.6%)**	**7 (14.9%)**	0	4 (5.1%)	2 (1.5%)
Increased blood level of liver enzymes	**5 (10.6%)**	3 (6.4%)	0	1 (1.3%)	3 (2.3%)
Low white blood cell count	**5 (10.6%)**	2 (4.3%)	0	0	0
A disease in which the body makes little to no insulin (type 1 diabetes)	**5 (10.6%)**	4 (8.5%)	5 (7.5%)	6 (7.6%)	**13 (10.0%)**
Infection with cytomegalovirus (a type of herpes virus)	4 (8.5%)	**6 (12.8%)**	0	0	0
Increased blood level of uric acid, a waste material from food digestion	2 (4.3%)	**5 (10.6%)**	1 (1.5%)	0	5 (3.8%)
Increased blood level of cholesterol	1 (2.1%)	**6 (12.8%)**	0	0	2 (1.5%)
Urinary tract infection	1 (2.1%)	**17 (36.2%)**	6 (9.0%)	2 (2.5%)	1 (0.8%)
Higher-than-normal blood sugar levels but not as high as in diabetes (prediabetes)	0	0	**7 (10.4%)**	0	0

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

The table below shows the number of patients from previous Advagraf studies who experienced a serious adverse reaction. These patients took at least 1 dose of Advagraf in this study.

Previous Advagraf Study in Which Patients Had Taken Part (total number of patients)	Number of Patients With Serious Adverse Reactions
Study 1 (out of 47 patients)	22 (46.8%)
Study 2 (out of 47 patients)	16 (34.0%)
Study 3 (out of 67 patients)	15 (22.4%)
Study 4 (out of 79 patients)	21 (26.6%)
Study 5 (out of 130 patients)	31 (23.8%)
Study 6 (out of 191 patients)	30 (15.7%)
Study 7 (out of 9 patients)	1 (0.1%)
Study 8 (out of 85 patients)	5 (5.9%)
Study 9 (out of 107 patients)	7 (6.5%)
Study 10 (out of 88 patients)	2 (2.3%)

A total of 18 patients died during the study. The deaths of 5 patients could have been related to Advagraf.

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 August 2012. 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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