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 Comparison of Effects of Standard Dose vs. Low Dose Advagraf® with IL-2 Receptor Antibody Induction, MMF and Steroids, with or without ACEi/ARB–Based Antihypertensive Therapy on Renal Allograft Histology, Function, and Immune Response

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 tacrolimus extended-release) is a prescription medicine that reduces the strength of the immune system. This is called an immunosuppressant medicine. It prevents the body from rejecting organ transplants. The standard treatment is to take Advagraf with supplemental immunosuppressant medicines. Standard Advagraf doses may cause kidney damage. Advagraf is a form of tacrolimus. Some researchers think that tacrolimus can cause damage to kidney transplants. If this is correct, then lowering the dose of Advagraf should lead to less kidney transplant damage. Therefore, this study compared the effects of a standard and low dose of Advagraf. (The low dose was lower than the standard dose.)

Most patients with kidney transplants have high blood pressure. Some types of high blood pressure medicines (called ACEis and ARBs) may slow kidney damage. Therefore, there was a need to study a new treatment combination for patients with kidney transplants. The combination included a low dose of Advagraf. And it included ACEis and/or ARBs.

This study was conducted in patients who received a kidney transplant. Patients took Advagraf (standard or low dose). Patients also took high blood pressure medicines (ACEis and/or ARBs or other types of high blood pressure medicines). This study looked at the effect of the study medicines on specific signs of kidney transplant damage. The study looked at the effect of the dose of Advagraf at 6 months after transplant surgery. And the study looked at the effect of the high blood pressure medicines at 24 months after transplant surgery. It was also important to find out what unwanted effects these patients had from the study medicines.

The study started in August 2009 and ended in April 2018. 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 each patient and the study doctors knew which dose of Advagraf that patient took (standard or low dose). And each patient and the study doctors knew which high blood pressure medicine that patient took (ACEis and/or ARBs or other types).

This study included women and men aged 18 years or older. In this study, these patients received their first or second transplant of 1 kidney. If it was their second transplant, their body had rejected their first transplant more than 1 year earlier. The patients and their kidney donors were different in (mismatched for) at least 1 immune system marker.

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 were picked for 1 of 4 treatment groups by chance alone. In addition, all patients took the same supplemental immunosuppressant medicines. The patients' blood pressure was checked regularly during this study. Their top number (systolic blood pressure) had to be less than 130 millimeters of mercury (mmHg). And their bottom number (diastolic blood pressure) had to be less than 80 mmHg.

- Group 1:
  - Advagraf (standard dose): Patients took Advagraf capsules (0.15 to 0.20 mg per kg body weight) once daily.
  - High blood pressure medicines (ACEi/ARB): Within 1 month after the transplant surgery, patients took ramipril capsules. If patients could not tolerate ramipril, they took irbesartan tablets.
- Group 2:
  - Advagraf (standard dose): Patients took Advagraf capsules (0.15 to 0.20 mg per kg body weight) once daily.
  - High blood pressure medicines (no ACEi or ARB): Patients only took high blood pressure medicines if they developed high blood pressure after transplant surgery. The medicines that they then took were not ramipril or irbesartan or related medicines and were not aliskiren.
- Group 3:
  - Advagraf (low dose): Patients took Advagraf capsules (0.05 to 0.15 mg per kg body weight) once daily.
  - High blood pressure medicines (ACEi/ARB): The high blood pressure medicines in group 3 were the same as in group 1.
- Group 4:
  - Advagraf (low dose): Patients took Advagraf capsules (0.05 to 0.15 mg per kg body weight) once daily.
  - High blood pressure medicines (no ACEi or ARB): The timing and type of high blood pressure medicines in group 4 were the same as in group 2.

Patients took study medicines for up to 60 months (5 years).

This study took place at 13 clinics in Canada. 281 patients were in the study. Out of these patients, 279 patients took at least 1 dose of study medicine.

	Number of Patients
Age Group Aged between 19 and 81 years	 279
Sex Men Women	 190 89

What Were the Study Results?

This study in patients with a kidney transplant looked at the effect of the study medicines on specific signs of kidney transplant damage. The study looked at the effect of the dose of Advagraf at 6 months after transplant surgery. And the study looked at the effect of the high blood pressure medicines at 24 months after transplant surgery.

The study showed that at 6 months after transplant surgery, 35 out of 95 patients (36.8%) who took a low dose of Advagraf had specific signs of kidney transplant damage. And 34 out of 86 patients (39.5%) who took a standard dose of Advagraf had the same signs. It did not matter if patients took a standard or low dose of Advagraf. The number of patients with kidney transplant damage compared to all treated patients was similar. This means that lowering the dose of Advagraf did not have an effect on kidney transplant damage. (A statistical test showed that the small percent difference between the 2 groups was likely to be due to chance.)

At 24 months after transplant surgery, 46 out of 84 patients (54.8%) who took ACEi and/or ARB high blood pressure medicines had specific signs of kidney transplant damage. And 46 out of 79 patients (58.2%) who took other types of high blood pressure medicines had the same signs. A statistical test showed that the difference between the 2 groups was likely to be due to chance. This means that the difference was not due to the different types of high blood pressure medicine.

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.

The table below shows the most common adverse events experienced by patients who took at least 1 dose of study medicine in this study.

Adverse Event	Advagraf (out of 279 patients)
Any adverse event	278 (99.6%)
Diarrhea	195 (69.9%)
Swelling of the ankles, feet or fingers	176 (63.1%)
Uncontrolled trembling or shaking movements in one or more parts of the body	155 (55.6%)
Nausea or the urge to vomit	154 (55.2%)
Decreased blood level of phosphate	153 (54.8%)
Decreased blood level of magnesium	149 (53.4%)
Vomiting	122 (43.7%)
Constipation	120 (43.0%)
Pain associated with the surgery and study investigations or treatments	120 (43.0%)
Headache or head pain	113 (40.5%)

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.

272 patients (97.5%, or 272 out of 279 patients) experienced an adverse reaction.

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

135 patients (48.4%, or 135 out of 279 patients) experienced a serious adverse reaction in this study.

12 patients died during the study. The deaths of 4 of the 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 December 2018. You can find this summary and more information about this study online at http://www.astellasclinicalstudy results.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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