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)

Clinical Study Report Erratum

PMR-EC-1213

28 SEP 2018

The purpose of this erratum is to:

- Correct errors detected after final clinical study report approval

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1 ABSTRACT

Was:

There were 60 patients (3.0%) with at least 1 Investigator reported serious ADR. The incidence was higher for patients from the ADVANCE and ADHERE trials, 24 (2.9%) and 22 (3.7%) patients, respectively, than for patients from the DIAMOND trial, 14 (2.3%).

Is amended to:

There were 68 patients (3.4%) with at least 1 Investigator reported serious ADR. The incidence was higher for patients from the ADVANCE and ADHERE trials, 28 (3.4%) and 26 (4.4%) patients, respectively, than for patients from the DIAMOND trial, 14 (2.3%).

Rationale:

The number of patients with at least 1 Investigator reported serious ADR was incorrect overall.

2 SECTION 10.3.3 Adverse Drug Reactions

Was:

A separate listing presented the subset of AEs identified as ADRs (AEs which met any of the special situations as defined in Section 9.4.3.3 and/or were possibly or probably related to tacrolimus. There were 116 patients with at least 1 Investigator reported ADR.

Is amended to:

A separate listing presented the subset of AEs identified as ADRs (AEs which met any of the special situations as defined in Section 9.4.3.3 and/or were possibly or probably related to tacrolimus. There were 117 patients with at least 1 Investigator reported ADR.

Rationale:

The number of patients with at least 1 Investigator reported ADR was incorrect.

3 SECTION 10.3.3.1 Non Serious Adverse Drug Reactions

Was:

Of the 116 patients with at least 1 Investigator-reported ADR, 55 (2.7%) had at least 1 which was considered non serious. The incidence was highest for patients from the ADHERE trial (29, 4.9%), followed by patients from the ADVANCE trial (22, 2.7%) with a much lower incidence of patients from the DIAMOND trial (4, 0.6%). Table 98 lists individual non serious ADRs.

Table 98 Non Serious ADRs

Study	Patient	PT(s)
DIAMOND	[redacted]	Hot flush, Sleep disorder and Diabetes mellitus Liver function test abnormal Vaginal infection and Urinary tract infection (twice) Sepsis
ADVANCE	[redacted]	Actinic cheilitis Renal impairment Herpes zoster Epstein-Barr virus infection Nephropathy toxic Respiratory tract infection Alopecia Squamous cell carcinoma of head and neck Urinary tract infection Tremor Pneumonia Intestinal polyp, Upper respiratory tract infection and *Escherichia* urinary tract infection (twice) Squamous cell carcinoma Dermatitis bullous Cytomegalovirus infection Actinic keratosis Seborrhoeic keratosis Diarrhoea Diarrhoea Upper respiratory tract infection and Urinary tract infection Urinary tract infection (twice) Type 2 diabetes mellitus
ADHERE	[redacted]	Influenza and Nasopharyngitis Herpes zoster Squamous cell carcinoma of skin Polyomavirus test positive Herpes zoster and Urinary tract infection bacterial Skin papilloma, Oral herpes and Herpes zoster Aphthous stomatitis *Escherichia* urinary tract infection Oral candidiasis *Escherichia* urinary tract infection (twice) Diabetes mellitus *Escherichia* urinary tract infection Urinary tract infection *Escherichia* bacteraemia and *Escherichia* urinary tract infection (twice) Tremor Tremor Gastric cancer Urinary tract infection (twice) Bowen's disease, Skin cancer and Squamous cell carcinoma of skin Ophthalmic herpes zoster Oral herpes, Actinic keratosis and Basal cell carcinoma Nasopharyngitis and Tremor Nasopharyngitis and Rhinitis Nasopharyngitis Polyomavirus test positive Influenza Liver function test abnormal Tremor Nasopharyngitis, Anaemia and Staphylococcal bacteraemia

If Investigator causality was missing for an ADR sponsor causality was reported
ADR, adverse drug reaction; PT, preferred term
Source: Listing 16.2.7.2

Is amended to:

Of the 117 patients with at least 1 Investigator-reported ADR, 60 (3.0%) had at least 1 which was considered non serious. The incidence was highest for patients from the ADHERE trial (32, 5.5%), followed by patients from the ADVANCE trial (24, 2.9%) with a much lower incidence of patients from the DIAMOND trial (4, 0.6%). Table 98 lists individual non serious ADRs.

Table 98 Non Serious ADRs

Study	Patient	PT(s)
DIAMOND	[redacted]	Hot flush, Sleep disorder and Diabetes mellitus
		Liver function test abnormal
		Vaginal infection and Urinary tract infection (twice)
		Sepsis
ADVANCE		Actinic cheilitis
		Nephropathy toxic
		Renal impairment
		BK virus infection
		Herpes zoster
		Epstein-Barr virus infection
		Nephropathy toxic
		Respiratory tract infection
		Alopecia
		Squamous cell carcinoma of head and neck
		Urinary tract infection
		Tremor
		Pneumonia
		Intestinal polyp, Upper respiratory tract infection and *Escherichia* urinary tract infection (twice)
		Squamous cell carcinoma
		Dermatitis bullous
		Cytomegalovirus infection
		Actinic keratosis
		Seborrhoeic keratosis
		Diarrhoea
		Diarrhoea
		Upper respiratory tract infection and Urinary tract infection
		Urinary tract infection (twice)
		Type 2 diabetes mellitus
ADHERE		Influenza and Nasopharyngitis
		Herpes zoster
		Squamous cell carcinoma of skin
		Polyomavirus test positive
		Herpes zoster and Urinary tract infection bacterial
		Skin papilloma, Oral herpes and Herpes zoster
		Aphthous stomatitis
		Escherichia urinary tract infection
		Oral candidiasis
		Escherichia urinary tract infection (twice)
		Diabetes mellitus
		Escherichia urinary tract infection
		Urinary tract infection
		Escherichia bacteraemia and *Escherichia* urinary tract infection (twice)
		Tremor
		Tremor
		Renal impairment
		Urinary tract infection
		Gastric cancer
		Urinary tract infection (twice)
		Bowen's disease, Skin cancer and Squamous cell carcinoma of skin
		Ophthalmic herpes zoster
		Oral herpes
		Actinic keratosis and Basal cell carcinoma
		Nasopharyngitis and Tremor
		Nasopharyngitis and Rhinitis
		Nasopharyngitis
		Polyomavirus test positive
		Influenza
		Liver function test abnormal
		Tremor
		Nasopharyngitis, Anaemia and Staphylococcal bacteraemia

If Investigator causality was missing for an ADR sponsor causality was reported
ADR, adverse drug reaction; PT, preferred term
Source: Listing 16.2.7.2

Rationale:

The number of patients with at least 1 Investigator-reported non serious ADR was incorrect overall as was the non serious ADR incidence by feeder trial and the list of individual patients with a non serious ADR, by feeder trial, shown in the associated in-text table.

4 SECTION 10.3.3.2 Serious Adverse Drug Reactions

Was:

Of the 116 patients with at least 1 Investigator-reported ADR, 60 (3.0%) had at least 1 which was considered serious. The incidence was higher for patients from the ADVANCE and ADHERE trials, 24 (2.9%) and 22 (3.7%) patients, respectively, than for patients from the DIAMOND trial (14, 2.3%). Table 99 lists individual serious ADRs.

Table 99 Serious ADRs

Study	Patient	PT(s)
DIAMOND	[redacted]	Gastroenteritis radiation, Hyperventilation and Rectal adenocarcinoma
		Papillary thyroid cancer
		Colitis ulcerative (twice)
		Squamous cell carcinoma
		Acute prerenal failure
		Colitis ulcerative (twice)
		Upper respiratory tract infection bacterial
		Liver transplant rejection
		Renal failure
		Leukoencephalopathy
		Bile duct stenosis
		Toxicity to various agents
		Renal failure
		Squamous cell carcinoma of head and neck
ADVANCE		Granuloma
		Streptococcal sepsis
		Pyelonephritis acute
		Diabetes mellitus
		Glioblastoma
		Pneumonia
		Basal cell carcinoma (twice)
		Squamous cell carcinoma of head and neck
		Escherichia urinary tract infection, Bacterial pyelonephritis (twice), Pyelonephritis, Sepsis and Bronchitis
		Localised infection
		Cholangiocarcinoma
		Escherichia urinary tract infection
		Prostatic abscess and Septic shock
		Lung infection
		Renal failure acute and Influenza
		Pneumonia
		Viral infection
		Enteritis
		Pneumonia and Adenocarcinoma of colon
		Diarrhoea
		Escherichia urinary tract infection
		Urinary tract infection
		Pyelonephritis and Urosepsis
		Diarrhoea (twice)
ADHERE		Cytomegalovirus infection
		Gastroenteritis rotavirus
		Pneumonia
		Proteinuria, Blood creatinine increased, Lower respiratory tract infection bacterial, Renal failure acute and Lower respiratory tract infection viral
		Squamous cell carcinoma of skin and Urosepsis
		Basal cell carcinoma and Malignant melanoma in situ
		Adenocarcinoma and Metastasis
		Influenza, Squamous cell carcinoma of the oral cavity and Basal cell carcinoma
		Bronchopneumonia
		Diarrhoea (twice) and *Escherichia* urinary tract infection
		Complications of transplanted kidney (twice)
		Urinary tract infection
		Adrenal neoplasm
		Basal cell carcinoma, Squamous cell carcinoma of skin and Squamous cell carcinoma (3 times)
		Influenza
		Bronchopneumonia

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Study	Patient	PT(s)
ADHERE	[redacted]	Squamous cell carcinoma of head and neck
		Renal impairment
		Renal impairment
		Pneumonia
		Urosepsis and Pyelonephritis (twice)
		Erysipelas

If Investigator causality was missing for an ADR sponsor causality was reported
ADR, adverse drug reaction; PT, preferred term
Source: Listing 16.2.7.2

Is amended to:

Of the 117 patients with at least 1 Investigator-reported ADR, 68 (3.4%) had at least 1 which was considered serious. The incidence was higher for patients from the ADVANCE and ADHERE trials, 28 (3.4%) and 26 (4.4%) patients, respectively, than for patients from the DIAMOND trial, 14 (2.3%). Table 99 lists individual serious ADRs.

Table 99 Serious ADRs

Study	Patient	PT(s)
DIAMOND	[redacted]	Gastroenteritis radiation, Hyperventilation and Rectal adenocarcinoma
		Papillary thyroid cancer
		Colitis ulcerative (twice)
		Squamous cell carcinoma
		Acute prerenal failure
		Colitis ulcerative (twice)
		Upper respiratory tract infection bacterial
		Liver transplant rejection
		Renal failure
		Leukoencephalopathy
		Bile duct stenosis
		Toxicity to various agents
		Renal failure
		Squamous cell carcinoma of head and neck
ADVANCE		Granuloma
		Streptococcal sepsis
		Sepsis
		Pyelonephritis acute
		Diabetes mellitus
		Glioblastoma
		Lobar pneumonia
		Pneumonia
		Basal cell carcinoma (twice)
		Squamous cell carcinoma of head and neck
		Escherichia urinary tract infection, Bacterial pyelonephritis (twice) and Pyelonephritis
		Sepsis and Bronchitis
		Localised infection
		Cholangiocarcinoma
		Escherichia urinary tract infection
		Prostatic abscess and Septic shock
		Lung infection
		Renal failure acute and Influenza
		Pneumonia
		Viral infection
		Enteritis
		Pneumonia and Adenocarcinoma of colon
		Diarrhoea
		Escherichia urinary tract infection
		Urinary tract infection
		Pyelonephritis and Urosepsis
		Diarrhoea (twice)
		Adenocarcinoma of colon
ADHERE	[redacted]	Cytomegalovirus infection
		Gastroenteritis rotavirus
		Pneumonia
		Proteinuria, Blood creatinine increased, Lower respiratory tract infection bacterial, Renal failure acute and Lower respiratory tract infection viral
	[redacted]	Squamous cell carcinoma of skin and Urosepsis
		Basal cell carcinoma and Malignant melanoma in situ
		Adenocarcinoma and Metastasis
		Influenza, Squamous cell carcinoma of the oral cavity and Basal cell carcinoma
		Bronchopneumonia
		Renal impairment
		Squamous cell carcinoma of skin
		Basel cell carcinoma (twice), Small intestine carcinoma recurrent and Squamous cell carcinoma
		Respiratory tract infection
		Diarrhoea (twice) and *Escherichia* urinary tract infection
		Complications of transplanted kidney (twice)
		Urinary tract infection
		Adrenal neoplasm
		Basal cell carcinoma, Squamous cell carcinoma of skin and Squamous cell carcinoma (3 times)
		Influenza
		Bronchopneumonia

Table continued on next page

Study	Patient	PT(s)
ADHERE	[redacted]	Squamous cell carcinoma of head and neck
		Renal impairment
		Renal impairment
		Pneumonia
		Urosepsis and Pyelonephritis (twice)
		Erysipelas

If Investigator causality was missing for an ADR sponsor causality was reported
ADR, adverse drug reaction; PT, preferred term
Source: Listing 16.2.7.2

Rationale:

The number of patients with at least 1 Investigator-reported serious ADR was incorrect overall as was the serious ADR incidence by feeder trial and the list of individual patients with a serious ADR, by feeder trial, shown in the associated in-text table.

5 SECTION 10.3.5 Special Situations

Was:

There was 1 patient with a special situation: Patient [redacted], a [redacted] from the treatment arm 1 of the ADHERE trial who became pregnant [redacted] after transplantation (Listing 16.2.7.2).

For the special situation events defined in Section 9.4.3.3, no reports met the criteria for special situations of overdose, misuse, abuse, lack of efficacy, medical error, off -label use or occupational exposure.

Is amended to:

There were 5 patients who became pregnant, of which 4 were designated as a special situation but should not have been (Patients [redacted] and [redacted]) and 1 was not designated as a special situation (Patient [redacted]).

Patient [redacted], a [redacted] from the treatment arm 1 of the DIAMOND trial became pregnant [redacted] after transplantation.

Patient [redacted], a [redacted] from the treatment arm 1 of the ADVANCE trial became pregnant an unknown length of time after transplantation.

Patient [redacted], a [redacted] from the treatment arm 2 of the ADHERE trial became pregnant [redacted] after transplantation.

Patient [redacted], a [redacted] from the treatment arm 1 of the ADHERE trial who became pregnant [redacted] after transplantation (after consent for the follow-up study).

Patient [redacted], a [redacted] from the treatment arm 1 of the ADVANCE trial became pregnant [redacted] after transplantation (after consent for the follow-up study).

Listing 16.2.7.1 shows the individual patient data. For the other special situation events defined in Section 9.4.3.3, no reports met the criteria for special situations of overdose, misuse, abuse, lack of efficacy, medical error, off-label use or occupational exposure.

Rationale:

It was considered necessary to report all occurrences of pregnancy but clarify that they were not special situations even if designated as such and also to clarify that no other reports of special situations met the relevant criteria for a special situation.

1 ABSTRACT

Title

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)

Keywords

Tacrolimus, Advagraf®, prolonged-release, Allograft, long-term outcomes

Rationale and background

Long-term graft survival is a challenge with approximately 50% of transplants failing after 10 years. However, emerging evidence showed that the prolonged-release formulation of tacrolimus (Advagraf) may improve patient adherence compared with immediate-release tacrolimus (Prograf®), reduce intra patient variability in tacrolimus exposure and produce more stable renal function. This long-term non interventional follow-up study of patients who received Advagraf immunosuppression following transplantation may provide important data to prescribers, patients and providers of the potential benefits of Advagraf in a real world setting in the long term.

Research question and objectives

The primary objective was to evaluate the impact of Advagraf on long-term graft survival in kidney and liver allograft recipients.

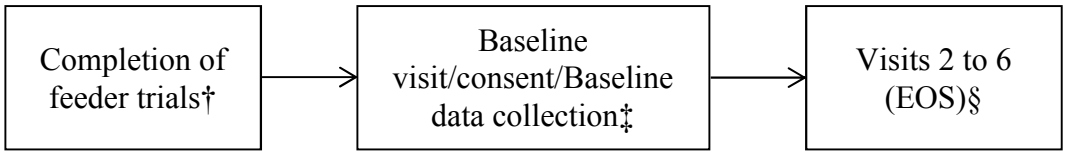
Study design

This was a multicenter long-term non interventional follow-up study of kidney and liver allograft recipients enrolled into previous Advagraf clinical trials (i.e., feeder trials).

Setting

Eligible patients who had participated in a feeder trial could enroll. These clinical trials comprised DIAMOND (PMR-EC-1106, liver transplant trial), ADVANCE (PMR-EC-1211) and ADHERE (PMR-EC-1212), both kidney transplant trials. Figure A 1 summarizes the study flow chart and Table A 1 summarizes feeder trial treatment arms.

Figure A 1 Study Flowchart



†For Selected Astellas-sponsored Advagraf clinical trials
‡1. Ongoing studies: Baseline visit was end of feeder trial visit; 2. Completed studies: Baseline visit was next scheduled review visit
§Annual data collection over 5 years post transplant
EOS, end of study

Table A 1 Feeder Trial Treatment Arms

Feeder Trial	Treatment Arms
DIAMOND PMR-EC-1106: liver transplant	1. Advagraf + MMF + corticosteroids (bolus) 2. Advagraf + MMF + basiliximab + corticosteroids (bolus) 3. Delayed Advagraf (delayed until Day 5) + MMF + basiliximab + corticosteroids (bolus)
ADVANCE PMR-EC-1211: kidney transplant	1. Advagraf + basiliximab + MMF + steroids (discontinued at 10 days) 2. Advagraf + basiliximab + MMF + steroids (optional intra op, bolus only)
ADHERE PMR-EC-1212: kidney transplant	1. Advagraf + MMF + steroid 2. Advagraf + MMF (withdrawn at Day 28) + steroids + sirolimus (from Day 28)

MMF, mycophenolate mofetil

Patients and study size

Adult patients were eligible if they had been assigned Advagraf treatment and had received a kidney or liver transplant in a feeder trial and provided informed consent for the current follow-up study. No power calculations for sample size estimation were performed. It was anticipated that up to 3000 patients would be enrolled into the follow-up study, from approximately 178 centers in Europe, Canada and Asia.

Variables and data sources

The primary variable was overall graft survival. Graft loss, for liver transplantation, was defined as retransplantation or death. For kidney transplantation, graft loss was defined as retransplantation, graft nephrectomy, death or as dialysis ongoing at end of study (EOS) or at the time of patient discontinuation from the study.

The following were secondary variables:

- Overall patient survival, defined as the time from transplantation to date of death from any cause. Patients alive at EOS or at the time of analysis were censored
- Renal function as calculated by estimated glomerular filtration rate (eGFR), using the 4-variable modification of diet in renal disease (MDRD4) and chronic kidney disease epidemiology collaboration (CKD-EPI) formulae
- Renal function assessed by estimated creatinine clearance (eCC) calculated with the Cockcroft and Gault formula
- Emergence of de novo donor specific antibody (DSA)
- Biopsy proven acute rejection (BPAR)
- Tacrolimus dose and formulation
- Tacrolimus trough level
- Current immunosuppressant regime – dose, formulation and any dose changes

The following were safety variables:

- Diagnosis of medical conditions of interest
- Diagnosis of infections of special interest
- Adverse events (AEs)
- Serum creatinine
- Weight

Feeder trials databases, serious adverse events, adverse drug reaction (ADR) worksheets and hospital medical records, were considered source documents.

Results

There were 2819 patients who were assigned a treatment and who received a transplant in 1 of the 3 feeder trials: 856 in the DIAMOND trial, 1125 in the ADVANCE trial, and 838 in the ADHERE trial. Following feasibility assessment, 140 sites took part in the study with an anticipated patient pool of approximately 2400.

Baseline Characteristics

Baseline characteristics were taken from the databases of the 3 feeder trials DIAMOND, ADVANCE and ADHERE) included in this follow-up study (ADDRESS).

There were 2819 patients who were assigned a treatment and who received a transplant in 1 of the 3 feeder trials: 856 in the DIAMOND trial, 1125 in the ADVANCE trial, and 838 in the ADHERE trial. Of the 2819 patients, 2018 patients (71.6%) were enrolled from 140 centers into the follow-up ADDRESS study for the final analysis of whom 1543 (76.5%) completed the feeder trials and 224 (11.1%) prematurely withdrew from the feeder trials.

The number of patients who died during the feeder trial or before they could be consented for the follow-up was 251 (12.4%) and the number of patients who died between the end of the feeder trail and the start of the follow-up study was 133 (4.7%).

Of the 2018 patients included in the follow-up study at time of the final analysis, 83.6% (1687/2018) completed the 5-year follow-up period (71.8%, 90.2%, and 86.9% for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively).

The demographic and baseline characteristics of the patients in the follow-up study were generally similar to those obtained for the respective feeder trial.

The mean (SD) recipient age was 54.3 (9.76), 50.5 (13.20) and 50.0 (13.40) years for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively. The majority of patients included in the follow-up patient set (FPS) were males (71.8%, 65.1% and 65.4% for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively).

The mean eGFR at the end of the feeder trial was 69.7, 49.6 and 54.5 mL/min/1.73 m^2 for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively. The proportion of patients at baseline (time of transplantation) with a positive cytomegalovirus status was 68.1%, 67.6% and 68.8% for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively. The corresponding figures for hepatitis B virus negative were 86.7%, 97.9% and 98.8%, respectively; for hepatitis C virus negative were 70.8%, 97.4% and 96.8%, respectively; and for human immunodeficiency virus negative were 99.4%, 99.5% and 98.5%, respectively.

Efficacy Results

The efficacy results, discussion and conclusion sections of this clinical study report for this final analysis will focus on the data obtained from 5 years post transplant.

DIAMOND

Graft Survival

The graft survival rate at 5 years post transplant was 73.5% for patients from the DIAMOND trial and the rates for each of the 3 treatment arms were similar: 74.7%, 71.5% and 74.5% for treatment arms 1, 2 and 3, respectively. At 1 and 3 years post transplant, 84.6% and 77.6% of patients had retained their graft, respectively.

The Cox proportional hazards model analysis showed that patients with positive hepatitis C virus (HCV) status had a higher hazard of graft loss than those with negative HCV status at baseline: hazard ratio (HR) 1.93 (95% confidence interval [CI]: 1.44, 2.58). There were no differences in the hazard of graft loss for randomized arms in the feeder trial (arms 1 vs 3 and arms 2 vs 3) for donor age (< 50 vs ≥ 50 years), donor type and gender.

Overall Survival

The estimate of the rate of overall patient survival at 5 years post transplant was 76.3% for patients from the DIAMOND trial, and the rates were similar across the 3 arms (78.6%, 73.8% and 76.7%), for treatments arms 1, 2 and 3, respectively. At 1 and 3 years post transplant, 86.8% and 80.3% of patients had overall survival, respectively.

The Cox proportional hazards model analysis showed that male patients had a higher hazard of death than females: HR (95% CI) 1.59 (1.10, 2.32). However, these results need to be interpreted with caution because most of the mortality occurred during the feeder trial during which the male and female mortality rates were similar, slightly more males than females had follow-up data, and the survival status for patients not included in the follow-up study could not be ascertained. The analysis also showed that patients with a positive baseline HCV status had a higher hazard of death than patients with a negative baseline HCV status: HR (95% CI) 2.00 (1.47, 2.74).

Estimated Glomerular Filtration Rate

The mean (SD) eGFR (by MDRD4) at the end of the feeder trial for the patients in the FPS was 69.7 (30.2) mL/min/1.73 m^2 for patients from the DIAMOND trial. At 5 years post transplant, the mean (SD) eGFR (MDRD4) was 61.5 (30.4) mL/min/1.73 m^2 for the DIAMOND trial. The mean eGFR (MDRD4) at 5 years post transplant was similar across the treatment arms. Although the mean eGFR at 6 months post transplant was higher in treatment arm 2 than in treatment arms 1 and 3, the eGFR appeared similar across the treatment arms from year 1 onwards, but the trend was lower in treatment arm 3 than in treatment arms 1 and 2 across the visits. Similar observations were made for eGFR by CKD-EPI and CC (Cockcroft-Gault).

Acute Rejection

The acute rejection (AR)-free survival rate was 78.7% at 5 years post transplant for patients from the DIAMOND trial. Most ARs occurred in the first 6 months post transplant (AR-free survival rate: 82.2%). The differences observed between the arms at 6 months post transplant were maintained until 5 years post transplant. The rates at 6 months were 80.0%, 86.8% and 79.7% in treatment arms 1, 2 and 3, respectively. At 5 years post transplant, the rate remained higher in treatment arm 2 (83.5%) than in treatment arms 1 (76.6%) and 3 (75.8%).

Biopsy Proven Acute Rejection

The BPAR-free survival rate was 81.9% at 5 years post transplant for patients from the DIAMOND trial. Most BPARs occurred in the first 6 months post transplant (BPAR-free survival rate: 84.8%), when the rate was higher in treatment arm 2 (89.0%) than in treatment arm 1 (82.2%) and treatment arm 3 (83.1%).

Donor Specific Antibody Status

For patients from the DIAMOND trial, only a few patients included in the analysis were assessed for DSA, and there was only 1 patient with a positive result (at 2 years post transplant).

Concomitant Immunosuppressive Medications

The proportion of patients who took at least 1 concomitant immunosuppressive medication was 64.2% for patients from the DIAMOND trial, mainly comprising mycophenolic acid derivatives (mycophenolic acid mofetil (CellCept) or mycophenolic acid sodium (Myfortic) (55.0% to 85.0%). Systemic corticosteroids were taken by 14.6% of the patients. The only other immunosuppressive medication taken by more than 5% of patients were ciclosporin (5.2%) and everolimus (8.4%). The incidence of concomitant immunosuppressive medications was similar in each treatment arm.

Tacrolimus Prolonged-Release

The mean (SD) of tacrolimus total daily dose (Advagraf formulation) was 0.063 mg/kg (0.04) at 1 year post transplant and 0.039 mg/kg (0.03) at 5 years post transplant for patients from the DIAMOND trial.

Duration of Tacrolimus from Transplantation

For the Advagraf formulation, the mean duration of tacrolimus from transplantation was 870 days for patients from the DIAMOND trial and was 876 days for the patients who switched from Advagraf to Prograf formulation. For the patients who switched from Advagraf to other tacrolimus formulations, the mean duration of other tacrolimus formulation treatment was 440 days but these results have to be interpreted with caution however because the subject numbers were low (n = 14).

ADVANCE

Graft Survival

The graft survival rate at 5 years post transplant was 88.1% for patients from the ADVANCE trial and the rates for each of the 2 treatment arms were similar: 86.2% and 89.9% for treatment arms 1 and 2, respectively. At 1 and 3 years post transplant, 93.8% and 91.8% of patients had retained their graft, respectively.

The Cox proportional hazards model analysis showed the hazard of graft loss was higher in patients whose donors were ≥ 50 years compared with those with donor age < 50 years: HR 2.13 (95% CI: 1.40, 3.23). The analyses also showed that the hazard of graft loss was lower in patients with a non-cadaveric donor type compared with those with a cadaveric donor type: HR 0.21 (95% CI: 0.08, 0.58). There were no differences in the hazard of graft loss for the randomized arms in the feeder trial or gender.

Overall Survival

The estimate of the rate of overall patient survival at 5 years post transplant was 94.4% for patients from the ADVANCE trial. The rate was 93.2% and 95.5%, for treatment arms 1 and 2, respectively. At 1 and 3 years post transplant, 97.8% and 96.2% of patients had overall survival, respectively.

The Cox proportional hazards model analysis showed that patients whose donors were aged ≥ 50 years had a higher hazard of death than those whose donors were aged < 50 years: HR (95% CI): 2.23 (1.16, 4.28).

Estimated Glomerular Filtration Rate

The mean (SD) eGFR (by MDRD4) at the end of the feeder trial for the patients in the FPS was 49.6 (19.7) mL/min/1.73 m^2 for patients from the ADVANCE trial. At 5 years post transplant, the mean (SD) eGFR (MDRD4) was 51.1 (22.4). The mean eGFR (MDRD4) obtained at 6 months post transplant (or up to Day 181) was 49.2 mL/min/1.73 m^2. The mean eGFR at year 1 (52.7 mL/min/1.73 m^2) through to year 5 (51.1 mL/min/1.73 m^2) post transplant was relatively stable. The mean eGFR was similar for the 2 treatment arms across the visits. The statistical analysis of eGFR calculated by the MDRD4 formula over time showed no differences between treatment arms at any year post transplant. Similar observations were made for eGFR by CKD-EPI and CC (Cockcroft-Gault).

Acute Rejection

The AR-free survival rate was 74.2% at 5 years post transplant for the patients from the ADVANCE trial. Most ARs occurred in the first 6 months post transplant and the differences observed between both arms at this time point were maintained until 5 years post transplant. The rate was higher in treatment arm 1 than in treatment arm 2 at all visits (82.1% vs 74.8% at 6 months post transplant and 76.9% vs 71.6% at 5 years post transplant).

Biopsy Proven Acute Rejection

The BPAR-free survival rate was 84.1% at 5 years post transplant for the patients from the ADVANCE trial. Most BPARs occurred in the first 6 months post transplant (BPAR-free survival rate: 88.8%), when the rate was higher in treatment arm 1 (91.3%) than in treatment arm 2 (86.4%).

Donor Specific Antibody Status

Of the 203 (24.9%), 179 (22.0%), 140 (17.2%) and 125 (15.4%) patients from the ADVANCE trial assessed at 1, 3, 4 and 5 years post transplant, 9 (4.4%), 13 (7.3%), 13 (9.4%) and 12 (9.6%), respectively, had DSA present. The group of patients with DSA assessments differed from one visit to the other.

Concomitant Immunosuppressive Medications

The proportion of patients who took at least 1 concomitant immunosuppressive medication was 92.9% for patients from the ADVANCE trial, mainly comprising mycophenolic acid derivatives (mycophenolic acid mofetil (CellCept) or mycophenolic acid sodium (Myfortic) (55.0% to 85.0%). Systemic corticosteroids were taken by 26.2% of the patients. The incidence of concomitant immunosuppressive medications was similar in each treatment arm.

Tacrolimus Prolonged-Release

The mean (SD) of tacrolimus total daily dose (Advagraf formulation) was 0.073 mg/kg (0.05) at 1 year post transplant and 0.060 mg/kg (0.04) at 5 years post transplant for patients from the ADVANCE trial.

Duration of Tacrolimus from Transplantation

For the Advagraf formulation, the mean duration of tacrolimus from transplantation was 1385 days for patients from the ADVANCE trial and was 886 days for the patients who switched from Advagraf to Prograf formulation. For the patients who switched from Advagraf to other tacrolimus formulations, the mean duration of other tacrolimus formulation treatment was 803 days but these results have to be interpreted with caution however because the subject numbers were low (n = 40).

ADHERE

Graft Survival

The graft survival rate at 5 years post transplant was 84.0% for patients from the ADHERE trial and the rates for each of the 2 treatment arms were similar: 89.3% and 87.6% for treatment arms 1 and 2, respectively At 1 and 3 years post transplant, 93.0% and 89.4% of patients had retained their graft, respectively.

The Cox proportional hazards model analysis showed that the categories within each of the variables had similar HRs for graft loss.

Overall Survival

The estimate of the rate of overall patient survival at 5 years post transplant was 90.8% for patients from the ADHERE trial, and the rate was similar across the 2 treatment arms, 91.9%

and 93.3%, for treatment arms 1 and 2, respectively. At 1 and 3 years post transplant, 97.8% and 94.3% of patients had overall survival, respectively.

The Cox proportional hazards model analysis showed no differences in hazard of death for the randomized arms in the feeder trial, donor age (<50 vs ≥50 years), donor type and gender.

Estimated Glomerular Filtration Rate

The mean (SD) eGFR (by MDRD4) at the end of the feeder trial for the patients in the FPS was 54.5 (21.7) mL/min/1.73 m^2 for patients from the ADHERE trial. At 5 years post transplant, the mean (SD) eGFR (MDRD4) was 52.5 (23.0) mL/min/1.73 m^2 for the ADHERE trial.

The mean eGFR (MDRD4) at 1 year post transplant was 55.0 mL/min/1.73 m^2 similar to the value at 5 years post transplant (52.5 mL/min/1.73 m^2). The mean eGFR was similar for the 2 treatment arms across the visits. The statistical analysis of eGFR calculated by the MDRD4 formula over time showed no differences between treatment arms at any year post transplant.

Similar observations were made for eGFR by CKD-EPI and CC (Cockcroft-Gault).

Acute Rejection

The AR-free survival rate was 77.4% at 5 years post transplant for the patients from the ADHERE trial. Most ARs occurred in the first 6 months post transplant and the differences observed between both arms at this time point 6 months were maintained until 5 years post transplant. The rate was slightly higher in treatment arm 1 across all visits.

Biopsy Proven Acute Rejection

The BPAR-free survival rate was 86.0% at 5 years post transplant for the patients from the ADHERE trial. Most BPARs occurred in the first 6 months post transplant (BPAR-free survival rate: 89.3%), when the rate was similar in treatment arm 1 (90.9%) and in treatment arm 2 (89.9%).

Donor Specific Antibody Status

Of the 77 (13.1%), 68 (11.6%) and 50 (8.5%) patients from the ADHERE trial assessed at 3, 4 and 5 years post transplant, 7 (9.1%), 7 (10.3%) and 6 (12.0%), respectively, had DSA present.

Concomitant Immunosuppressive Medications

The proportion of patients who took at least 1 concomitant immunosuppressive medication was 90.1% for patients from the ADHERE trial, mainly comprising mycophenolic acid derivatives (mycophenolic acid mofetil (CellCept) or mycophenolic acid sodium (Myfortic) (55.0% to 85.0%). As per protocol, 35.1% (206 out of 587) took sirolimus and the majority of these patients (192 out of 206) were in treatment arm 2. Thus, the percentage of patients in treatment arm 2 who remained on sirolimus in combination with reduced dose of Advagraf was 71% (192 out of 269). Systemic corticosteroids (for systemic use) were common (65.9% of patients). The only other immunosuppressive medication taken by more than 5% of

patients was azathioprine (6.6%). The rate of concomitant immunosuppressive medications use was similar in each treatment arm except for sirolimus as detailed above.

Tacrolimus Prolonged-Release

The mean (SD) of tacrolimus total daily dose (Advagraf formulation) was 0.069 mg/kg (0.05) at 1 year post transplant and 0.052 mg/kg (0.04) at 5 years post transplant for patients from the ADHERE trial.

Duration of Tacrolimus and Sirolimus from Transplantation

For the Advagraf formulation, the mean duration of tacrolimus from transplantation was 1361 days for patients from the ADHERE trial and was 840 days for the patients who switched from Advagraf to Prograf formulation. For the patients who switched from Advagraf to other tacrolimus formulations, the mean duration of other tacrolimus formulation treatment was 761 days but these results have to be interpreted with caution however because the subject numbers were low (n = 16).

Safety Results

Only safety data collected during the follow-up study (that started on or after the informed consent for the follow-up study) were reported. All safety data collected during the feeder trials had already been reported.

The overall incidence of patients with at least 1 AE was 573 (28.4%) and was 93 (15.1%), 269 (33.0%) and 211 (35.9%) for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively.

There were 60 patients (3.0%) with at least 1 Investigator-reported serious ADR. The incidence was higher for patients from the ADVANCE and ADHERE trials, 24 (2.9%) and 22 (3.7%) patients, respectively, than for patients from the DIAMOND trial, 14 (2.3%).

There were 3 patients (all from the ADHERE trial) with ADRs leading to death and they were considered tacrolimus-related. The incidence of ADRs of special interest was 5 (0.8%), 12 (1.5%) and 15 (2.6%) for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively. There were 5 patients (2, 1 and 2 from the DIAMOND, ADVANCE and ADHERE trials, respectively) with ADRs leading to discontinuation of tacrolimus.

The safety results suggested that Advagraf was generally well tolerated and raised no new safety issues.

Discussion

This report provides summary results of long-term follow-up data obtained on 71.6% of patients enrolled in 3 previous clinical trials on Advagraf (DIAMOND, ADVANCE and ADHERE).

Of the 2018 patients included in the follow-up study, 84% (1687/2018) completed the 5-year follow-up period. This represents 60% (1687/2819) of all the patients who received an organ transplant in a feeder trial.

Approximately 85%, 94% and 93% of the patients from the DIAMOND, ADVANCE and ADHERE trials, respectively, retained their graft at 1 year after transplantation. At 3 years post transplant, the estimated graft survival rate was 78%, 92% and 89%, respectively, and at 5 years past transplant the rate was 74%, 88% and 84%, respectively.

The overall patient survival rate was 80%, 96% and 94% at 3 years post transplant and 76%, 94% and 91% at 5 years post transplant for patients from the DIAMOND, ADVANCE and ADHERE trials, respectively.

The differences between the study arms observed at 6 months post transplant in AR and BPAR for the DIAMOND and ADVANCE trials remained relatively stable during the 5 years post transplant.

In each of the 3 feeder trials, renal function results were relatively stable between year 1 and year 5 post transplant. These results need to be interpreted with caution because not all the patients in the feeder trials had follow-up data obtained or remained on Advagraf throughout the period.

Sensitivity analyses of patients who remained on Advagraf throughout the 5-year period will provide a more robust assessment of the impact of Advagraf on long-term outcomes (graft survival, patient survival and renal function).

There were no new safety concerns identified during the follow-up study.

Marketing Authorization holder

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