SYNOPSIS

Name of Sponsor/Company: Astellas Pharma Europe Ltd.		
Name of Finished Product: FK506E (MR4)		
Name of Active Ingredient: Tacrolimus		

Title of Study: 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

Responsible Medical Officer/Coordinating Investigator: [redacted] as of 01 September 2007 [redacted]

Investigator(s): [redacted] Austria); [redacted] Austria); [redacted] Austria); [redacted] Australia); [redacted] Australia); [redacted] Australia); [redacted] Australia); [redacted] Belgium); [redacted] Belgium); [redacted] Belgium); [redacted] Belgium); [redacted] Belgium); [redacted] Belgium); [redacted] Belgium); [redacted] Belgium); [redacted] Brazil); [redacted] Brazil); [redacted] Brazil); [redacted] Brazil); [redacted] Canada); [redacted] Canada); [redacted] Canada); [redacted] Canada); [redacted] Canada); [redacted] Canada); [redacted] Switzerland); [redacted] Czech Republic); [redacted] Denmark); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Germany); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Spain); [redacted] Finland); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] France); [redacted] UK); [redacted] UK); [redacted] UK); [redacted] UK); [redacted] UK); [redacted] UK); [redacted] Hungary); [redacted] Ireland); [redacted] Ireland); [redacted] Italy); [redacted] Italy); [redacted] Italy); [redacted]

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Study Center(s): 128 centers in the following 24 countries enrolled subjects in the study: Australia = 4, Austria = 3, Belgium = 10, Brazil = 5, Canada = 8, Czech Republic = 1, Denmark = 1, Finland = 1, France = 20, Germany = 16, Great Britain = 7, Hungary = 1, Ireland = 2, Italy = 12, Mexico = 2, The Netherlands = 2, New Zealand = 1, Poland = 4, Republic of South Africa = 6, Russia = 4, Spain = 14, Sweden = 2, Switzerland = 1, USA = 1
Publication (reference): Alloway R et al. Conversion of stable heart transplant recipients from twice daily Prograf® to once daily modified release tacrolimus. The World Transplant Congress, 22-27 July 2006, Boston, USA, p. 383, Abstr. 939; Van Hooff JP et al. Three-year experience with tacrolimus once-daily prolonged release in kidney, liver and heart recipients. International Congress of the Transplantation Society, 10-14 August 2008, Sydney, Australia, p. 185-186, Abstr. 530

Study Period: **Date of First Enrollment:** 24 February 2003 **Date of Last Evaluation:** 7 October 2009	**Phase of Development:** Phase III

Objectives: The objective of this study is to assess the safety and efficacy of FK506E (MR4) as long- term treatment in transplant recipients who have participated in one of the phase II pharmacokinetic or phase III studies on MR4 and have received at least one dose of study medication.
Study Design: This is a phase III, multicenter, open, prospective, single-arm study of MR4 in transplant recipients previously enrolled in phase II *de novo* kidney, phase II *de novo* liver, phase II kidney conversion, phase II heart conversion, phase III *de novo* liver and phase III *de novo* kidney clinical trials sponsored by Astellas Pharma Europe Ltd. (previously Astellas GmbH). In *de novo* studies subjects received MR4 (prolonged-release hard capsule formulation for once daily administration of tacrolimus) as the primary immunosuppressant following organ allograft transplantation. In conversion studies stable subjects on long-term immunosuppressive therapy with commercial Prograf® were converted to receive MR4 instead of Prograf®. In study PMR-EC-1209, subjects with cyclosporine-related side effects were converted from cyclosporine-A to MR4.

The endpoints for this study were analyzed using the date of entry into the present study as start date and not the date of transplantation or time of conversion to MR4.

Table 1: Previous MR4 Studies Followed up in Study FG-506-14-02

Phase II					
FG-506-11-01	**FG-506E-12-01**	**FG-506E-12-02**	**FG-506-15-02**		
de novo liver	*de novo* kidney	kidney conversion†	heart conversion†		
Phase III					
FG-506E-11-03	**FG-506E-12-03**	**PMR-EC-1210**	**PMR-EC-1105**	**PMR-EC-1205**	**PMR-EC-1209**
de novo liver	*de novo* kidney	*de novo* kidney	liver conversion†	kidney conversion†	kidney conversion‡

† Conversion from Prograf® to MR4. ‡ Conversion from cyclosporine A to MR4.

Study visits were scheduled for baseline/day 1 and thereafter at least every 3 months, with a time window of ± 14 days, until MR4 was launched in the respective country.
The end-of-study visit was defined as the last scheduled study visit or the time a subject was discontinued prematurely from the study.

Diagnosis and Main Criteria for Inclusion: Transplant recipients who participated in one of the previous phase II pharmacokinetic or phase III studies with MR4 and who received at least one dose of MR4 were eligible for entry into this study.

Number of Subjects (planned and analyzed): The exact number of subjects to be enrolled was dependent on the recruitment figures in the previous phase II pharmacokinetic and phase III studies. This final analysis provides data on the Full Analysis Set which comprised 850 organ allograft recipients from a phase II *de novo* liver study (FG-506-11-01; N=47), a phase II *de novo* kidney study (FG-506E-12-01; N=47), a phase II conversion study in kidney (FG-506E-12-02; N=67), a phase II conversion study in heart (FG-506-15-02; N=79), a phase III *de novo* study in liver (FG-506E-11-03; N=130), a phase III *de novo* kidney study (FG-506-12-03; N=191), a phase III conversion study in liver (PMR-EC-1105; N=85), a phase III conversion study in kidney (PMR-EC-1205; N=107), and a phase III conversion study in kidney (PMR-EC-1209; N=88). Also included are 9 subjects from a previous phase III *de novo* kidney study (PMR-EC-1210). All subjects received at least 1 dose of MR4 during the course of the study.

Test Product, Dose and Mode of Administration: The first dose of MR4 given at enrollment was to be the same as the last dose in the previous study. The investigator was thereafter permitted to adjust the dose and modify the MR4 dose regimen as deemed necessary to minimize adverse events and maintain effective immunosuppression. MR4 capsules were taken orally, once daily in the morning only and were to be swallowed with fluid (preferably water) on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal.

Lot Numbers:

Table 2: Batch Numbers of Study Medication MR4

MR4	Batch Numbers	Expiry Date
0.5 mg	[redacted]	August 2005
		October 2005
		October 2006
		October 2007
		June 2008
		November 2008
		November 2009
1 mg		March 2005
		July 2005
		September 2005
		April 2006
		June 2006
		July 2006
		October 2007
		February 2008
		April 2008
		June 2008
		November 2008
		October 2009
		February 2010
5 mg		July 2005
		August 2005
		September 2005
		July 2006
		August 2006
		September 2006
		August 2007
		September 2007
		April 2008
		October 2008
		November 2008
		January 2009
		October 2009
		January 2010

Concomitant immunosuppressive therapy: If steroids, mycophenolate mofetil (MMF) or azathioprine were administered at enrollment, the dosage was to be maintained during the course of this study where possible unless otherwise clinically indicated. Administration of rapamycin was not allowed.

Duration of Study and Treatment: Subjects remained in the study until MR4 was launched in the respective country. Study visits were scheduled for baseline/day 1 and thereafter at least every 3 months; the date of visit 1 was equal to the date of the last visit of the previous study. The dose of MR4 being taken at enrollment was to be maintained; dose adjustments deemed necessary to minimize adverse events and maintain effective immunosuppression were permitted.

Criteria for Evaluation: The primary endpoints were patient and graft survival. The secondary endpoints for efficacy were the incidence of and time to first biopsy-confirmed acute rejection episode; the secondary endpoint for safety was the incidence of adverse events.

Statistical Methods: Analyses of efficacy and safety were based on the Full Analysis Set which included all subjects who received at least one dose of study medication MR4 within one of the 4 phase II pharmacokinetic or one of the 6 phase III studies and within this study.
All parameters were summarized using appropriate descriptive statistics, i.e. number (%) of subjects (n) for categorical variables, and mean, standard deviation, median, minimum, maximum for continuous variables. Where appropriate, summaries were provided over time.

Subject and graft survival and incidence of and time to biopsy confirmed acute rejection were analyzed using Kaplan-Meier procedures.

RESULTS:

Analysis Sets and Subject Disposition: In total, 850 subjects participated in the study, 725 subjects (85.3%) completed the study. The number of deaths during the study was 18 of 850 (2.1%). The rate of premature study withdrawal was 12.6% (107 of 850 subjects) with a majority of all subjects withdrawn during the first 12 months of the study. An adverse event was the most common reason for premature study withdrawal.
Included are 9 subjects from previous study PMR-EC-1210; at the time of production of this report, this study was still in progress. As the number of subjects from that study is small, summary tables were not developed. Important efficacy and safety results from these 9 subjects are presented in the text body of this summary.

Demographics: The average age of subjects was 49.5 years and 68.5% of subjects were male. The age range was 21 to 77 years at enrollment in all subjects and in general male subjects were slightly older than female subjects. The overwhelming majority of subjects, 92%, were Caucasian.

Study Drug Administration: Mean total daily doses of MR4 (mg/kg) on day 1 of this study were slightly higher in subjects previously enrolled in phase II *de novo* studies than in phase II conversion studies. Mean total daily doses of MR4 showed a steady decrease during this study in subjects in previous *de novo* studies and remained relatively unchanged in those subjects in previous conversion studies. At end of study (EOS; 66 months or 5.5 years after start of study), the mean daily dose was similar across phase II studies and ranged between 0.06 and 0.08 mg/kg. Mean daily doses of MR4 at EOS were slightly lower in male subjects than in female subjects previously enrolled in phase II *de novo* studies. Mean daily doses at EOS were similar between male and female subjects in previous conversion study FG-506E-12-02 and slightly lower in male subjects than in female subjects in previous study FG-506-15-02.
Mean total daily doses of MR4 were similar across the phase III *de novo* and conversion studies at day 1 and remained relatively unchanged during the study. At EOS, the mean daily MR4 dose was 0.02 to 0.04 mg/kg lower in male subjects than in female subjects in all previous phase III studies. In subjects in the previous PMR-EC-1210 study, daily doses of MR4 at day 1 were slightly higher than doses in the other 5 phase III studies attributable to the shorter time elapsed between transplantation and study entry.

Efficacy Results:

Table 3A): Efficacy Endpoints at Month 60, by Previous Phase II Study

	***De Novo* Studies**		**Conversion Studies**	
	FG-506-11-01 (Liver) N = 47	**FG-506E-12-01 (Kidney) N = 47**	**FG-506E-12-02 (Kidney) N = 67**	**FG-15-02 (Heart) N = 79**
Graft survival†, %	90.9	100	92.2	90.3
Subject survival†, %	90.9	100	93.6	90.3
Freedom from biopsy-confirmed acute rejection†, %	92.6	93.2	100	87.0
Biopsy-confirmed acute rejection, n (%)	3 (6.4)	3 (6.4)	0	9 (11.4)

Table 3B): Efficacy Endpoints at Month 12, by Previous Phase III Study

	***De Novo* Studies**		**Conversion Studies**		
	FG-506E-11-03 (Liver) N = 130	**FG-506E-12-03 (Kidney) N = 191**	**PMR-EC-1105 (Liver) N=85**	**PMR-EC-1205 (Kidney) N=107**	**PMR-EC-1209 (Kidney) N=88**
Graft survival†, %	99.2	98.9	100	99.0	100
Subject survival†, %	99.2	100	100	100	100
Freedom from biopsy-confirmed acute rejection†, %	96.1	99.5	100	100	97.7
Biopsy-confirmed acute rejection, n (%)	5 (3.8)	1 (0.5)	0	0	1 (1.1)

† Overall estimated rates (Kaplan-Meier Method).

The overall incidence of graft loss was 2.8% (24 grafts lost of 850 subjects). Nine of 24 grafts lost were due to graft-related causes. Overall, no differences between males and females in graft loss were found. In previous studies FG-506-11-01 and FG-506E-12-03, proportionately more graft losses occurred in female than in male subjects.

For subjects from previous study PMR-EC-1210, there were no cases of graft loss, subject death, or biopsy-confirmed acute rejection during the study.

Safety Results: The most commonly affected system organ class, in which the incidence of adverse events regardless of relationship to MR4 administration was highest, was infections and infestations with an incidence ranging from 17% to 81% across previous studies. Infections and infestations was also the most commonly affected system organ class in which the incidence of serious adverse events was highest. Incidences ranged from 6% to 40% across previous studies. The incidence of all adverse events decreased over time. There were no marked differences in the pattern and incidence of adverse events reported in males and females.

18 of 850 subjects (2.1%) died during the study; 14 subjects were from the previous phase II and 4 subjects from the previous phase III studies. The details of these deaths are provided in the following table.

Table 4: Summary of Deaths

Patient number	Sex	Cause of death MedDRA preferred term (investigator term)	Relationship to study drug†	Day of death
Death during study				
FG-506-11-01 (Phase II *de novo* liver)				
[redacted]	Female	Acute respiratory failure [redacted]	Possible	9
[redacted]	Female	Acute respiratory distress syndrome [redacted]	Definitely not	500
[redacted]	Male	Hepatic function abnormal [redacted]	Highly probable	224
[redacted]	Female	Astrocytoma [redacted]	Possible	386
FG-506E-12-02 (Phase II conversion kidney)				
[redacted]	Male	Pulmonary embolism [redacted]	Unlikely	434
[redacted]	Male	Lung neoplasm malignant [redacted]	Possible	872
[redacted]	Male	Operative hemorrhage [redacted]	Unlikely	895
[redacted]	Male	Cerebrovascular accident [redacted]	Unlikely	127
FG-506-15-02 (Phase II conversion heart)				
[redacted]	Male	Sudden death [redacted]	Unlikely	889
[redacted]	Male	Renal insufficiency [redacted]	Definitely not	1426
[redacted]	Male	Pulmonary embolism [redacted]	Definitely not	1426
[redacted]	Male	B-cell unclassifiable lymphoma high grade [redacted]	Possible	285
[redacted]	Male	Hypoglycemia [redacted]	Definitely not	856
[redacted]	Male	Hepatic cirrhosis [redacted]	Definitely not	1774
FG-506E-11-03 (Phase III *de novo* liver)				
[redacted]	Male	Cardiac disorder [redacted]	Unlikely	312
[redacted]	Female	Hepatic failure [redacted]	Definitely not	567
[redacted]	Male	Esophageal varices hemorrhage [redacted]	Unlikely	656
FG-506E-12-03 (Phase III conversion kidney)				
[redacted]	Male	Myocardial infarction [redacted]	Unlikely	406

† Investigator assessed.

There were no deaths in the phase II *de novo* kidney subjects (study FG-506E-12-01) and no deaths in the phase III liver conversion (PMR-EC-1105) and kidney conversion subjects (PMR-EC-1205 and PMR-EC-1209). Five subjects died in year 1, 6 subjects died in year 2, 4 subjects died in year 3, 2 subjects died in year 4, and 1 subject died in year 5.

Across phase II studies, infections, metabolism and nutrition disorders, and gastrointestinal disorders were the most commonly affected system organ classes, with a higher overall incidence of adverse events in the phase II *de novo* than in the phase II conversion studies. Across phase III studies, infections and infestations, metabolism and nutrition disorders, and gastrointestinal disorders were also the most commonly affected system organ classes, also with incidences higher in the *de novo* than in the conversion studies. Adverse events were reported in 2 of 9 subjects in the previous PMR-EC-1210 study. One subject experienced 2 non-fatal serious adverse events.

At end of study, creatinine clearance was the lowest for previous phase II studies FG-506-12-01 and FG-506-12-02 resulting in the highest serum creatinine levels, as can be expected. In the previous phase III studies, creatinine clearance was lowest for the kidney transplant recipients (resulting in the highest serum creatinine levels) and highest for the liver *de novo* and conversion studies.

The overall incidence of malignancies ranged from 1.1% (PMR-EC-1209) to 20.3% (FG-506-15-02); higher incidences of malignancies were found in subjects in the previous phase II studies: these subjects had been receiving immunosuppressive treatment for a longer time period (approximately 6 years) compared to subjects in the phase III studies (approximately 1 year). The most common type of malignancy reported was basal cell carcinoma.
The overall incidence of any glucose metabolism disorders in subjects without a pre-existing condition ranged from 1.3% (PMR-EC-1205) to 45.7% (FG-506-11-01). Incidences were generally higher in the *de novo* studies. The most commonly reported glucose metabolism disorder was hyperglycemia with an incidence of 1.3% to 20.0%. A difference in the incidence of glucose metabolism disorders between males and females is difficult to interpret due to the low number of female subjects; however, there appears to be no sex-related differences in the incidence of glucose metabolism disorders.

CONCLUSIONS:

- MR4 proved to be safe and effective in subjects from previous phase II *de novo* and conversion studies and previous phase III *de novo* and conversion studies.
- Efficacy was maintained in terms of subject and graft survival and prevention of biopsy confirmed acute rejection in the phase II *de novo* and conversion studies as well as the phase III *de novo* and conversion studies.
- The safety profile of MR4 was comparable to the established Prograf® safety profile, and the adverse events reported during the study were consistent with the known safety profile of systemic tacrolimus.
- The incidence of glucose metabolism disorders was higher in *de novo* studies and there were no apparent differences in incidence between males and females.
- As expected, higher incidences of malignancies were seen in subjects maintained over a longer period of time on immunosuppressive medications; basal cell carcinoma was the most commonly reported type of malignancy.
- Although there were some differences in the incidence of individual adverse events, there was no marked effect of sex on the safety profile of MR4.

Date of Report: 02 Sep 2015