SYNOPSIS

Name of Sponsor: Astellas Pharma Europe Ltd		
Name of Finished Product: Tacrolimus		
Name of Active Ingredient: FK506E (MR4)		
Title of Sub-Study: An open-label, single centre study to assess the effect of food on the relative bioavailability of orally administered tacrolimus modified release formulation, FK506E (MR4), in stable kidney transplant recipients.		
Principal Investigator: [redacted]		
Study Center: [redacted], The Netherlands		
Publication (reference): None		
Study Initiation Date: 24 Sep 2007 (1st PK patient enrolled) **Study Completion Date:** 20 Dec 2007 (Last PK assessment)		**Phase of Development:** 1

Objective:
The objective of the sub-study was to assess the pharmacokinetic (PK) and relative bioavailability of tacrolimus when orally administered as FK506E (MR4) capsules in stable kidney transplant recipients under fasted and non-fasted conditions.

Study Design:
This was a four-period, fixed-sequence, non-randomized, sub-study of FG-506-14-02.

Diagnosis and Main Criteria for Inclusion:
Stable kidney transplant patients aged ≥ 18 years. Subjects who were participating in clinical study FG-506-14-02, and were being treated with FK506E (MR4) under fasted conditions and had no changes in any of their medications for at least 7 days.

Number of Subjects (planned and analyzed):
Twenty-four patients with 2 complete, evaluable profiles were required to investigate the effect of a standard continental breakfast on the oral bioavailability of tacrolimus. Twenty-seven patients were enrolled in the study to allow for any possible patient withdrawals. Twenty-seven subjects entered and completed the sub-study. Data for all subjects were included in the pharmacokinetic analyses.

Test Product, Dose And Mode of Administration:
FK506E (MR4) was administered orally at dose levels between 1 and 15 mg (the same dose levels as used in clinical study FG-506-14-02). FK506E (MR4) was supplied as 0.5, 1 and 5 mg capsules.

Duration of Study and Treatment:
On Day -14/-7 to Day -1 (Period 1), patients were screened to ensure that enrolment criteria were met. On Days 1 to 7 (Period 2, Profile 1) patients continued to take daily FK506E (MR4) capsules under fasted conditions (at least 1 hour before or 2 to 3 hours after a meal). On Days 8 to 14 (Period 3, Profile 2) patients took daily doses of FK506E (MR4) capsules under non-fasted conditions (within 5 minutes after completion of a standard continental breakfast). On Days 15 to 21 (Period 4) patients returned to taking FK506E (MR4) capsules under fasted conditions, however, there was no PK blood sampling in Period 4.

Criteria for Pharmacokinetic Evaluation:
Blood samples for the analysis of whole blood concentrations of tacrolimus.

Statistical Methods:
Summary statistics were presented for the PK data, as appropriate.
PK parameters were analyzed using a mixed model. Least squares means were calculated for the non-fasted and fasted states. Mean differences between the non-fasted and fasted states were

calculated with 90% confidence intervals (CIs).

PHARMACOKINETIC RESULTS:

The pharmacokinetic parameters and associated statistical analysis of tacrolimus following administration of FK506E (MR4) under fasted and non-fasted conditions are presented in the following table:

Parameter	FK506E (MR4) non-fasted (N=27)	FK506E (MR4) fasted (N=27)	Ratio of geometric LS means (90% CI) non-fasted:fasted
AUC_{0-24} (ng.h/mL)	173 (23.2)	201 (16.6)	0.861 (0.815-0.910)
C_{max} (ng/mL)	11.5 (37.4)	14.1 (24.1)	0.815 (0.742-0.896)
C_{min} (ng/mL)	5.21 (20.7)	5.87 (15.7)	0.888 (0.842-0.936)
C_{24} (ng/mL)	5.32 (20.7)	6.09 (14.3)	0.873 (0.825-0.925)
t_{max}[a] (h)	3.00 (2.00-8.00)	2.00 (1.00-4.00)	NC

Geometric mean (CV%) data are presented
N = Total number of patients
NC = Not calculated
[a] Median (min–max)

CONCLUSIONS:

- Mean AUC_{0-24} for tacrolimus was 14% lower following administration of FK506E (MR4) after a standard continental breakfast compared to under fasted conditions. Individual changes in AUC_{0-24} ranged from +29% to -38% under non-fasted compared to fasted conditions.
- Mean C_{max} for tacrolimus was 19% lower following administration of FK506E (MR4) after a standard continental breakfast compared to under fasted conditions.
- The time to reach the maximum concentration of tacrolimus was 1 hour later when FK506E (MR4) was administered after a standard continental breakfast (3 hours) compared to under fasted conditions (2 hours).
- Regression analysis demonstrated good correlation between AUC_{0-24} and C_{24} for tacrolimus following administration in the non-fasted and fasted states.

Date of Report: 18 March 2009